Supplementary Appendix

Contents

Table S1 – Covariate Details for Adjusted Analyses

Study	Covariates Used For		
	As-Treated Analysis	**Missing Data Analysis**	**Dose Response Analysis**
ILLUMENATE Pivotal NCT01858428 NCT01912937	Age, Sex, Black race, Smoking, BMI, CAD, Hypertension, Hyperlipidemia, Diabetes, History of MI, renal insufficiency, BL statin use, BL antithrombotic use, Rutherford (<3, >=3), number of target lesions, lesion location, percent stenosis, minimal lumen, vessel diameter, lesion length, BL ABI	Randomization assignment, diabetes	Age, Sex, Smoking, BMI, CAD, Hypertension, Hyperlipidemia, Diabetes, History of MI, Rutherford (<3, >=3)
ILLUMENATE EU RCT NCT02110524	Age, Sex, Smoking, BMI, CAD, Hypertension, Hyperlipidemia, Diabetes, History of MI, renal insufficiency, BL statin use, BL antithrombotic use, Rutherford (<3, >=3), number of target lesions, lesion location, percent stenosis, minimal lumen, vessel diameter, lesion length, BL ABI	Randomization assignment, lesion length	Age, Sex, Smoking, CAD, Hypertension, Hyperlipidemia, Diabetes, History of MI
IN.PACT SFA I/II NCT01175850 NCT01566461	Age, Sex, Smoking, BMI, CAD, Hypertension, Hyperlipidemia, Diabetes, renal insufficiency, BL statin use, BL antiplatelet use, BL ACE Inhibitor/ARB use, BL Beta Blocker use, BL anticoagulant use, Rutherford (<3, >=3), number of target lesions, lesion location, percent stenosis, minimal lumen, vessel diameter, lesion length, BL ABI	Randomization assignment	Age, Sex, Smoking, BMI, Hypertension, Hyperlipidemia, Diabetes, Rutherford (<3, >=3)
IN.PACT SFA Japan NCT01947478	Age, Sex, Smoking, BMI, CAD, Hypertension, Hyperlipidemia, Diabetes, renal insufficiency, Rutherford (<3, >=3), percent stenosis, minimal lumen, vessel diameter, lesion length, BL ABI	Randomization assignment	Age, Sex, Smoking, BMI, Hypertension, Hyperlipidemia, Diabetes, BL ABI
Levant I NCT00930813	Age, Sex, Smoking, BMI, Hypertension, Hyperlipidemia, Diabetes, History of MI, BL statin use, BL antithrombotic use, BL antiplatelet use, BL ACE Inhibitor/ARB use, BL Beta Blocker use, BL anticoagulant use, Rutherford (<3, >=3), lesion location, percent stenosis, vessel diameter, lesion length	Randomization assignment	Age, Sex, Smoking, Hypertension, Hyperlipidemia, History of MI

Levant II NCT01412541	Age, Sex, Black race, Smoking, BMI, CAD, Hypertension, Hyperlipidemia, Diabetes, History of MI, renal insufficiency, BL statin use, BL antithrombotic use, BL antiplatelet use, BL ACE Inhibitor/ARB use, BL Beta Blocker use, Rutherford (<3, >=3), number of target lesions, lesion location, percent stenosis, minimal lumen, vessel diameter, lesion length, BL ABI	Randomization assignment, age	Age, Sex, Smoking, BMI, CAD Hypertension, Hyperlipidemia, Diabetes, History of MI, Rutherford (<3, >=3),
Lutonix Japan Not Registered	Age, Sex, Smoking, BMI, Hypertension, Hyperlipidemia, Diabetes, History of MI, renal insufficiency, BL statin use, BL ACE Inhibitor/ARB use, BL Beta Blocker use, Rutherford (<3, >=3), number of target lesions, lesion location, percent stenosis, minimal lumen, vessel diameter, lesion length, BL ABI	Randomization assignment	Age, Sex, Smoking, BMI, Hypertension, Hyperlipidemia, Diabetes, renal insufficiency, BL ABI
Zilver PTX NCT00120406	Age, Sex, Black race, Smoking, BMI, CAD, Hypertension, Hyperlipidemia, Diabetes, History of MI, Rutherford (<3, >=3), number of target lesions, lesion location, percent stenosis, minimal lumen, vessel diameter, lesion length, BL ABI	Randomization assignment, diabetes, BL ABI	Age, Sex, BMI, CAD, Hypertension, Hyperlipidemia, Diabetes, History of MI

Three analyses employed covariate adjustment: the adjusted as-treated analysis, missing data sensitivity analysis and dose-response analysis. The list of covariates to be considered for these analyses were pre-specified in the statistical analysis plan.

For the adjusted as-treated analysis and dose-response analysis, a covariate was omitted from the propensity score model for a particular study if it was not collected in that study or if there were model fit issues due to a limited number of observed levels of a covariate. Missing values for covariates were handled via multiple imputation by study. As treated analysis utilized stratfiication on propensity score quintile. Dose-response analysis utilized propensity score weighting based on a generalized logit model.

For the missing data analysis, only the randomization arm and specific covariates for a study that were found to be predictive of the outcome and of censoring (based on $p<0.15$) were included in the model for weighting based on the inverse probability of censoring.

Table S2 – Patient Characteristics

		ILLUMENATE Pivotal	ILLUMENATE EU RCT	IN.PACT SFA I/II	IN.PACT Japan	Levant I	Levant II	Lutonix Japan	Zilver PTX RCT
Age (years)	Mean ± SD (N)	68.8 ± 10.2 (300)	67.3 ± 9.1 (294)	67.6 ± 9.4 (331)	73.6 ± 7.0 (100)	68.3 ± 9.2 (101)	68.2 ± 9.7 (476)	74.5 ± 9.6 (109)	67.8 ± 10.1 (474)
Sex	F	41.3% (124/300)	28.9% (85/294)	34.1% (113/331)	24.0% (24/100)	36.6% (37/101)	37.0% (176/476)	34.9% (38/109)	35.2% (167/474)
	M	58.7% (176/300)	71.1% (209/294)	65.9% (218/331)	76.0% (76/100)	63.4% (64/101)	63.0% (300/476)	65.1% (71/109)	64.8% (307/474)
BMI	Mean ± SD (N)	29.0 ± 6.0 (300)	27.3 ± 4.7 (290)	27.6 ± 4.8 (331)	22.9 ± 3.1 (100)	27.2 ± 4.5 (100)	28.7 ± 5.2 (476)	23.4 ± 3.6 (109)	28.3 ± 5.4 (474)
Hispanic/Latino	No	76.3% (229/300)	99.7% (293/294)	48.3% (160/331)	0% (0/100)	0% (0/101)	0% (0/476)	100.0% (109/109)	82.3% (390/474)
	Yes	12.7% (38/300)	0% (0/294)	6.0% (20/331)	0% (0/100)	0% (0/101)	0% (0/476)	0% (0/109)	5.5% (26/474)
	Unknown/ Missing	11.0% (33/300)	0.3% (1/294)	45.6% (151/331)	100.0% (100/100)	100.0% (101/101)	100.0% (476/476)	0% (0/109)	12.2% (58/474)
Black/African American		18.0% (54/300)	0.3% (1/294)	7.3% (24/331)	0% (0/100)	0% (0/101)	5.3% (25/476)	0% (0/109)	10.1% (48/474)
Race Unknown/ Not Reported		4.7% (14/300)	0.3% (1/294)	45.6% (151/331)	100.0% (100/100)	100.0% (101/101)	4.2% (20/476)	0% (0/109)	12.2% (58/474)
Smoking Status	Active/ Current	35.7% (107/300)	49.7% (146/294)	37.8% (125/331)	28.0% (28/100)	34.7% (35/101)	34.7% (165/476)	22.9% (25/109)	31.6% (150/474)
	Previous	45.7% (137/300)	38.1% (112/294)	29.3% (97/331)	54.0% (54/100)	33.7% (34/101)	45.6% (217/476)	49.5% (54/109)	53.6% (254/474)

		ILLUMENATE Pivotal	ILLUMENATE EU RCT	IN.PACT SFA I/II	IN.PACT Japan	Levant I	Levant II	Lutonix Japan	Zilver PTX RCT
	Never	18.7% (56/300)	12.2% (36/294)	32.9% (109/331)	18.0% (18/100)	31.7% (32/101)	19.7% (94/476)	27.5% (30/109)	14.6% (69/474)
	Unknown	0% (0/300)	0% (0/294)	0% (0/331)	0% (0/100)	0% (0/101)	0% (0/476)	0% (0/109)	0.2% (1/474)
Diabetes	No	49.7% (149/300)	62.9% (185/294)	56.8% (188/331)	42.0% (42/100)	52.5% (53/101)	57.1% (272/476)	53.2% (58/109)	54.2% (257/474)
	Yes	50.3% (151/300)	37.1% (109/294)	43.2% (143/331)	58.0% (58/100)	47.5% (48/101)	42.9% (204/476)	46.8% (51/109)	45.8% (217/474)
CAD	No	77.7% (233/300)	82.0% (241/294)	61.9% (205/331)	79.0% (79/100)	0% (0/101)	50.6% (241/476)	0% (0/109)	80.8% (383/474)
	Yes	22.3% (67/300)	18.0% (53/294)	31.7% (105/331)	17.0% (17/100)	0% (0/101)	49.4% (235/476)	0% (0/109)	19.2% (91/474)
	Unknown/ Missing	0% (0/300)	0% (0/294)	6.3% (21/331)	4.0% (4/100)	100.0% (101/101)	0% (0/476)	100.0% (109/109)	0% (0/474)
Hypertension	No	6.3% (19/300)	20.7% (61/294)	9.7% (32/331)	14.0% (14/100)	8.9% (9/101)	11.3% (54/476)	12.8% (14/109)	14.8% (70/474)
	Yes	93.7% (281/300)	79.3% (233/294)	90.3% (299/331)	86.0% (86/100)	91.1% (92/101)	88.7% (422/476)	87.2% (95/109)	85.2% (404/474)
Hyperlipidemia	No	11.3% (34/300)	36.7% (108/294)	16.3% (54/331)	27.0% (27/100)	35.6% (36/101)	11.6% (55/476)	33.0% (36/109)	27.0% (128/474)
	Yes	88.7% (266/300)	63.3% (186/294)	83.7% (277/331)	73.0% (73/100)	64.4% (65/101)	88.4% (421/476)	67.0% (73/109)	73.0% (346/474)
Renal Insufficiency	No	87.0% (261/300)	95.2% (280/294)	90.9% (301/331)	90.0% (90/100)	0% (0/101)	88.4% (421/476)	94.5% (103/109)	0% (0/474)

		ILLUMENATE Pivotal	ILLUMENATE EU RCT	IN.PACT SFA I/II	IN.PACT Japan	Levant I	Levant II	Lutonix Japan	Zilver PTX RCT
	Yes	12.3% (37/300)	4.1% (12/294)	7.6% (25/331)	10.0% (10/100)	0% (0/101)	5.9% (28/476)	5.5% (6/109)	0% (0/474)
	Unknown/ Missing	0.7% (2/300)	0.7% (2/294)	1.5% (5/331)	0% (0/100)	100.0% (101/101)	5.7% (27/476)	0% (0/109)	100.0% (474/474)
Prior MI	No	78.7% (236/300)	86.1% (253/294)	0% (0/331)	0% (0/100)	86.1% (87/101)	80.9% (385/476)	27.5% (30/109)	80.8% (383/474)
	Yes	21.3% (64/300)	13.9% (41/294)	0% (0/331)	0% (0/100)	13.9% (14/101)	19.1% (91/476)	13.8% (15/109)	19.2% (91/474)
	Unknown/ Missing	0% (0/300)	0% (0/294)	100.0% (331/331)	100.0% (100/100)	0% (0/101)	0% (0/476)	58.7% (64/109)	0% (0/474)
Rutherford Category (dichotomized)	Unknown/ Missing	0% (0/300)	0.7% (2/294)	0% (0/331)	0% (0/100)	0% (0/101)	0% (0/476)	0% (0/109)	0.4% (2/474)
	<=3	95.7% (287/300)	97.6% (287/294)	94.6% (313/331)	96.0% (96/100)	93.1% (94/101)	92.0% (438/476)	99.1% (108/109)	90.7% (430/474)
	>3	4.3% (13/300)	1.7% (5/294)	5.4% (18/331)	4.0% (4/100)	6.9% (7/101)	8.0% (38/476)	0.9% (1/109)	8.9% (42/474)
ABI (baseline)	Mean ± SD (N)	0.8 ± 0.2 (293)	0.7 ± 0.2 (280)	0.8 ± 0.2 (315)	0.8 ± 0.2 (100)	NA	0.7 ± 0.2 (462)	0.7 ± 0.2 (109)	0.7 ± 0.2 (461)
ACE/ARB Use (baseline)	No	0% (0/300)	0% (0/294)	68.9% (228/331)	0% (0/100)	16.8% (17/101)	31.3% (149/476)	33.9% (37/109)	0% (0/474)
	Yes	0% (0/300)	0% (0/294)	31.1% (103/331)	0% (0/100)	83.2% (84/101)	68.7% (327/476)	66.1% (72/109)	0% (0/474)
	Unknown/ Missing	100.0% (300/300)	100.0% (294/294)	0% (0/331)	100.0% (100/100)	0% (0/101)	0% (0/476)	0% (0/109)	100.0% (474/474)

		ILLUMENATE Pivotal	ILLUMENATE EU RCT	IN.PACT SFA I/II	IN.PACT Japan	Levant I	Levant II	Lutonix Japan	Zilver PTX RCT
Statin Use (baseline)	No	24.7% (74/300)	34.4% (101/294)	68.3% (226/331)	0% (0/100)	28.7% (29/101)	22.3% (106/476)	45.9% (50/109)	0% (0/474)
	Yes	75.3% (226/300)	65.6% (193/294)	31.7% (105/331)	0% (0/100)	71.3% (72/101)	77.7% (370/476)	54.1% (59/109)	0% (0/474)
	Unknown/ Missing	0% (0/300)	0% (0/294)	0% (0/331)	100.0% (100/100)	0% (0/101)	0% (0/476)	0% (0/109)	100.0% (474/474)
Antithrombotic Use (baseline)	No	2.3% (7/300)	3.1% (9/294)	6.9% (23/331)	0% (0/100)	12.9% (13/101)	5.5% (26/476)	0% (0/109)	0% (0/474)
	Yes	97.7% (293/300)	96.9% (285/294)	93.1% (308/331)	100.0% (100/100)	87.1% (88/101)	94.5% (450/476)	100.0% (109/109)	0% (0/474)
	Unknown/ Missing	0% (0/300)	0% (0/294)	0% (0/331)	0% (0/100)	0% (0/101)	0% (0/476)	0% (0/109)	100.0% (474/474)
Beta Blocker Use (baseline)	No	0% (0/300)	0% (0/294)	74.9% (248/331)	0% (0/100)	27.7% (28/101)	43.1% (205/476)	74.3% (81/109)	0% (0/474)
	Yes	0% (0/300)	0% (0/294)	25.1% (83/331)	0% (0/100)	72.3% (73/101)	56.9% (271/476)	25.7% (28/109)	0% (0/474)
	Unknown/ Missing	100.0% (300/300)	100.0% (294/294)	0% (0/331)	100.0% (100/100)	0% (0/101)	0% (0/476)	0% (0/109)	100.0% (474/474)
Bailout Stent Used	No	94.0% (282/300)	83.0% (244/294)	90.9% (301/331)	96.0% (96/100)	0% (0/101)	95.6% (455/476)	96.3% (105/109)	0% (0/474)
	Yes	6.0% (18/300)	16.0% (47/294)	9.1% (30/331)	4.0% (4/100)	0% (0/101)	4.4% (21/476)	3.7% (4/109)	0% (0/474)
	Unknown/ Missing	0% (0/300)	1.0% (3/294)	0% (0/331)	0% (0/100)	100.0% (101/101)	0% (0/476)	0% (0/109)	100.0% (474/474)

		ILLUMENATE Pivotal	ILLUMENATE EU RCT	IN.PACT SFA I/II	IN.PACT Japan	Levant I	Levant II	Lutonix Japan	Zilver PTX RCT
Lesion Location/s (per subject)	Unknown	0% (0/300)	1.0% (3/294)	0.3% (1/331)	0% (0/100)	0% (0/101)	0% (0/476)	0% (0/109)	0% (0/474)
	PPA	6.7% (20/300)	7.5% (22/294)	3.3% (11/331)	1.0% (1/100)	44.6% (45/101)	9.0% (43/476)	10.1% (11/109)	4.0% (19/474)
	PPA/SFA	0% (0/300)	5.1% (15/294)	3.6% (12/331)	1.0% (1/100)	0% (0/101)	0% (0/476)	0.9% (1/109)	3.8% (18/474)
	SFA	93.3% (280/300)	86.4% (254/294)	92.7% (307/331)	98.0% (98/100)	55.4% (56/101)	91.0% (433/476)	89.0% (97/109)	92.2% (437/474)
Number of Target Lesions	Unknown/ Missing	0% (0/300)	0% (0/294)	0.3% (1/331)	0% (0/100)	0% (0/101)	0% (0/476)	0% (0/109)	0% (0/474)
	1	100.0% (300/300)	86.7% (255/294)	98.5% (326/331)	100.0% (100/100)	100.0% (101/101)	97.7% (465/476)	97.2% (106/109)	94.9% (450/474)
	2	0% (0/300)	13.3% (39/294)	1.2% (4/331)	0% (0/100)	0% (0/101)	2.3% (11/476)	2.8% (3/109)	5.1% (24/474)
Percent stenosis	Mean ± SD (N)	74.2 ± 16.9 (300)	79.2 ± 15.9 (329)	81.2 ± 14.9 (334)	80.4 ± 13.5 (100)	89.6 ± 10.5 (101)	80.6 ± 14.8 (476)	79.8 ± 14.4 (112)	79.1 ± 17.0 (498)
Minimal Lumen Diameter (mm)	Mean ± SD (N)	1.3 ± 0.9 (300)	1.0 ± 0.8 (329)	0.9 ± 0.8 (334)	0.9 ± 0.7 (100)	NA	0.9 ± 0.8 (476)	1.0 ± 0.7 (112)	1.1 ± 0.9 (498)
Vessel Diameter (mm)	Mean ± SD (N)	5.0 ± 1.0 (300)	5.0 ± 0.8 (329)	4.7 ± 0.8 (334)	4.8 ± 0.7 (100)	5.1 ± 0.6 (101)	4.8 ± 0.8 (476)	4.8 ± 0.7 (112)	5.0 ± 0.9 (498)
Lesion Length (mm)	Mean ± SD (N)	82.7 ± 45.7 (299)	71.6 ± 52.0 (329)	89.6 ± 49.4 (330)	90.7 ± 58.8 (100)	87.1 ± 37.3 (101)	62.8 ± 41.0 (475)	63.9 ± 46.1 (109)	54.1 ± 40.5 (498)

NA = not applicable (not collected or unavailable). Race not reported or unknown as assumed to be race other than Black / African American

Table S3 – Kaplan-Meier Cumulative Mortality

Study	Paclitaxel					Control			
	Time Point	Mortality Rate [95% HW CB][1]	Deaths	At Risk	Censored	Mortality Rate [95% HW CB][1]	Deaths	At Risk	Censored
All Studies	365	2.1% [0.5%, 8.3%]	28	1281	73	1.9% [0.2%, 17.7%]	15	741	47
	730	7.0% [4.6%, 10.6%]	90	1102	190	4.7% [1.8%, 11.9%]	35	648	120
	1095	9.8% [7.2%, 13.2%]	121	905	356	7.6% [4.2%, 13.6%]	53	523	227
	1460	13.5% [10.8%, 16.9%]	153	673	556	10.6% [6.8%, 16.1%]	68	427	308
	1825	18.3% [15.4%, 21.8%]	187	282	913	13.7% [9.7%, 19.1%]	82	201	520
ILLUMENATE Pivotal	365	2.0% [0.0%, 59.8%]	4	192	4	1.0% [0.0%, 100.0%]	1	98	1
	730	6.8% [2.2%, 20.1%]	13	172	15	7.2% [1.3%, 34.5%]	7	88	5
	1095	9.1% [3.8%, 20.7%]	17	139	44	10.4% [3.2%, 30.8%]	10	67	23
	1460	11.9% [5.7%, 23.7%]	20	46	134	16.7% [7.5%, 34.6%]	13	27	60
	1825	16.0% [9.0%, 27.5%]	22	10	168	21.3% [10.2%, 41.5%]	14	4	82
ILLUMENATE EU RCT	365	1.4% [0.0%, 88.3%]	3	204	15	1.6% [0.0%, 100.0%]	1	61	10
	730	6.4% [2.1%, 18.8%]	13	186	23	3.3% [0.1%, 85.7%]	2	59	11
	1095	9.0% [4.0%, 19.4%]	18	156	48	8.2% [1.7%, 35.7%]	5	44	23
	1460	13.7% [8.0%, 23.1%]	25	106	91	8.2% [1.7%, 35.7%]	5	33	34
	1825	19.5% [12.9%, 28.8%]	31	53	138	18.1% [7.8%, 38.8%]	8	17	47
IN.PACT SFA I/II	365	1.9% [0.1%, 33.5%]	4	204	12	0.0% [NE]	0	109	2
	730	7.7% [3.7%, 16.0%]	16	187	17	0.9% [0.0%, 100.0%]	1	104	6
	1095	10.3% [5.8%, 17.8%]	21	173	26	1.9% [0.0%, 52.6%]	2	101	8
	1460	11.8% [7.2%, 19.1%]	24	159	37	7.1% [2.6%, 18.6%]	7	89	15
	1825	14.6% [9.8%, 21.6%]	29	40	151	10.2% [5.1%, 19.8%]	10	19	82

Study	Paclitaxel					Control			
	Time Point	Mortality Rate [95% HW CB][1]	Deaths	At Risk	Censored	Mortality Rate [95% HW CB][1]	Deaths	At Risk	Censored
IN.PACT Japan	365	0.0% [NE]	0	67	1	0.0% [NE]	0	32	0
	730	6.0% [2.0%, 17.4%]	4	62	2	3.1% [0.1%, 62.9%]	1	28	3
	1095	6.0% [2.0%, 17.4%]	4	31	33	6.6% [1.4%, 28.7%]	2	12	18
	1460	NE	4	0	64	NE	2	0	30
	1825	NE	4	0	64	NE	2	0	30
Levant 1	365	4.2% [0.4%, 34.4%]	2	45	2	8.0% [0.7%, 62.1%]	4	43	5
	730	8.4% [2.8%, 24.0%]	4	30	15	8.0% [0.7%, 62.1%]	4	34	14
	1095	NE	4	0	45	NE	5	0	47
	1460	NE	4	0	45	NE	5	0	47
	1825	NE	4	0	45	NE	5	0	47
Levant 2	365	2.0% [0.1%, 34.5%]	6	281	29	2.7% [0.3%, 25.0%]	4	144	12
	730	7.4% [3.2%, 16.6%]	21	257	38	5.5% [1.7%, 16.6%]	8	133	19
	1095	10.3% [5.6%, 18.5%]	29	245	42	6.2% [2.2%, 16.7%]	9	130	21
	1460	16.2% [11.0%, 23.6%]	45	224	47	9.1% [4.5%, 18.0%]	13	123	24
	1825	19.7% [14.2%, 26.8%]	54	103	159	12.1% [7.1%, 20.1%]	17	55	88
Lutonix Japan	365	1.4% [0.1%, 29.4%]	1	70	0	2.9% [0.1%, 75.0%]	1	34	3
	730	2.8% [0.6%, 13.1%]	2	20	49	8.7% [2.4%, 28.8%]	3	7	28
	1095	NE	2	0	69	NE	3	0	35
	1460	NE	2	0	69	NE	3	0	35
	1825	NE	2	0	69	NE	3	0	35
Zilver PTX RCT	365	3.5% [0.5%, 24.1%]	8	218	10	1.7% [0.0%, 65.3%]	4	220	14
	730	7.8% [3.1%, 18.8%]	17	188	31	4.1% [0.7%, 21.3%]	9	195	34
	1095	12.4% [6.9%, 21.7%]	26	161	49	8.3% [3.5%, 19.0%]	17	169	52

Study	Paclitaxel					Control			
	Time Point	Mortality Rate [95% HW CB][1]	Deaths	At Risk	Censored	Mortality Rate [95% HW CB][1]	Deaths	At Risk	Censored
	1460	14.1% [8.4%, 23.2%]	29	138	69	10.0% [4.9%, 20.0%]	20	155	63
	1825	22.7% [16.1%, 31.5%]	41	76	119	11.9% [6.4%, 21.4%]	23	106	109

HW CB = Hall-Wellner Confidence Bands. NE = not estimable.

Table S4 – Tipping Point Analysis

	Control Power Term				
Treatment Power Term	**0.6**	**0.8**	**1.0**	**1.2**	**1.4**
0.6	1.31 (1.04, 1.66)	1.24 (0.99, 1.56)	1.19 (0.95, 1.49)	1.14 (0.91, 1.42)	1.10 (0.89, 1.37)
0.8	1.37 (1.09, 1.73)	1.31 (1.04, 1.64)	1.25 (1, 1.57)	1.2 (0.96, 1.49)	1.15 (0.93, 1.43)
1.0	1.44 (1.15, 1.81)	1.38 (1.11, 1.73)	1.32 (1.06, 1.64)	1.26 (1.01, 1.57)	1.20 (0.97, 1.49)
1.2	1.50 (1.20, 1.88)	1.43 (1.15, 1.79)	1.39 (1.11, 1.73)	1.31 (1.05, 1.63)	1.26 (1.02, 1.56)
1.4	1.57 (1.25, 1.96)	1.49 (1.20, 1.87)	1.44 (1.15, 1.79)	1.37 (1.11, 1.7)	1.31 (1.06, 1.62)

Values displayed are Hazard Ratios (95% confidence interval).

The tipping point analysis imputed follow-up and events for censored subjects based on the observed treatment group specific survival distribution. Scenarios where the results are "tipped" to a non-significant finding are highlighted.

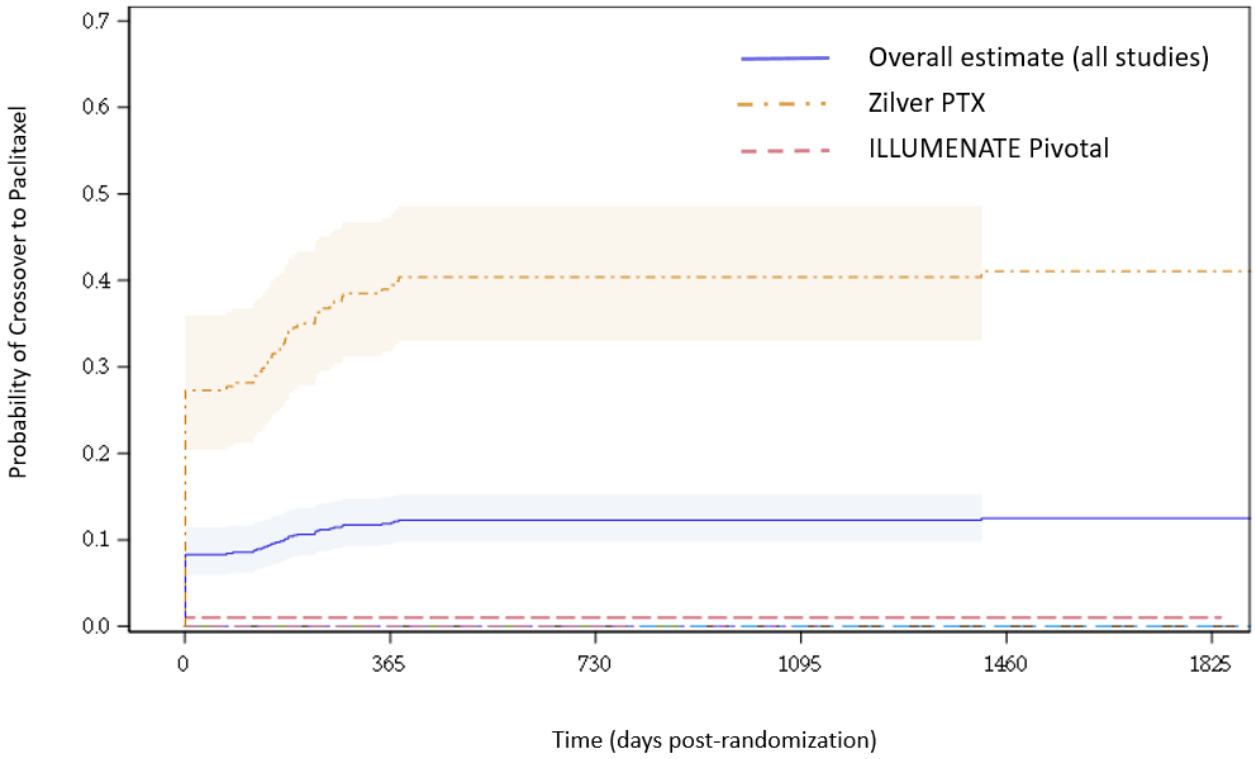
The imputed event rate was varied by a power parameter to include possible scenarios where the rate in subjects with missing data was lower or higher than the observed treatment group rate. The power parameter was applied to the observed survival distribution; parameter values less than one indicate a lower event rate than observed, whereas values greater than one indicate a higher event rate observed. The analysis model was a Cox proportional hazards model with a fixed treatment effect and no stratification. Imputation was done separately for each study.

References:

S1. Zhao Y, Herring AH, Zhou H, Ali MW, and Koch GW. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. Journal of Biopharmaceutical Statistics, 2014;24(2):229–2534.

S2. Fink S, Sensitivity Analyses for Informative Censoring in Time-to-Event Clinical Trials, 2015, https://epub.ub.uni-muenchen.de/25582/1/MA_FinkSimon.pdf.

Figure S1 – Control Crossover to Paclitaxel



Incidence of crossover of control patients to paclitaxel containing treatments. The Zilver PTX study employed a secondary randomization to paclitaxel for subjects initially assigned to a non-paclitaxel control but for whom suboptimal initial results were observed. One early crossover was observed for the ILLUMENATE Pivotal study. Data on post-index procedure crossover to paclitaxel for control subjects was not necessarily consisently or completely collected. There was no crossover for all other studies.

Figure S2 – Subgroup Results – Demographics

	Hazard Ratio (95% CI)	Interaction P-value
Age 64 and under	1.57 (0.93, 2.68)	0.746
Age 65 - 74	1.42 (0.91, 2.22)	
Age 75 and over	1.24 (0.83, 1.85)	
Female	1.35 (0.88, 2.09)	0.984
Male	1.35 (0.98, 1.86)	
Black	1.38 (0.58, 3.29)	0.285
Other	1.50 (1.10, 2.04)	
Unknown	0.89 (0.49, 1.62)	
BMI Less than Median	1.08 (0.75, 1.57)	0.09
BMI Median or Greater	1.70 (1.18, 2.45)	
Smoker - Active/Current	1.33 (0.85, 2.09)	0.935
Smoker - Previous	1.31 (0.90, 1.90)	
Smoker - Never	1.48 (0.83, 2.66)	
Smoker - Unknown	NA	

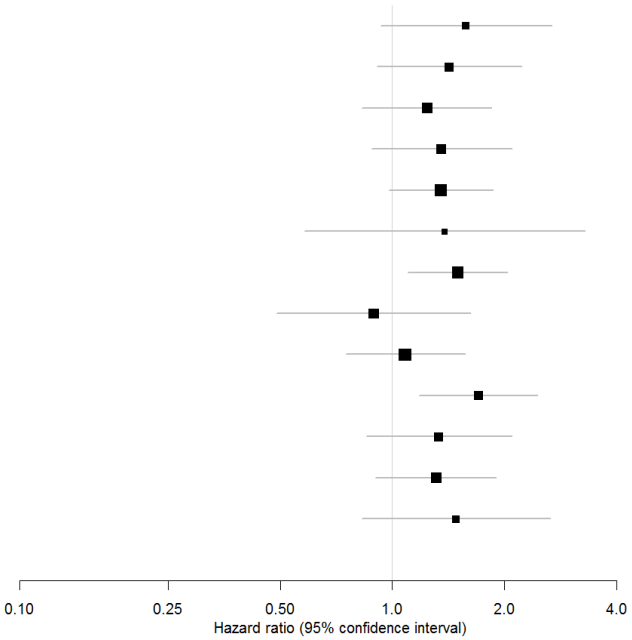


Figure S3 – Subgroup Results – Medical History

		Hazard Ratio (95% CI)	Interaction P-value
Diabetes			0.556
	Yes	1.45 (1.01, 2.09)	
	No	1.25 (0.87, 1.81)	
Coronary Artery Disease			0.173
	Yes	1.52 (0.96, 2.40)	
	No	1.40 (1.00, 1.97)	
	Unknown	0.60 (0.23, 1.51)	
Hypertension			0.828
	Yes	1.33 (1.01, 1.75)	
	No	1.44 (0.67, 3.11)	
Hyperlipidemia			0.170
	Yes	1.49 (1.10, 2.01)	
	No	0.99 (0.58, 1.68)	
Renal insufficiency/eGFR			0.792
	Yes	1.23 (0.54, 2.81)	
	No	1.29 (0.92, 1.81)	
	Unknown	1.56 (0.98, 2.48)	
Previous myocardial infarction			0.595
	Yes	1.02 (0.54, 1.91)	
	No	1.48 (1.07, 2.03)	
	Unknown	1.30 (0.70, 2.42)	
Prior PCI			0.994
	Yes	1.30 (0.35, 4.80)	
	No	1.37 (0.83, 2.26)	
	Unknown	1.35 (0.99, 1.84)	
Previous Peripheral Revascularization			0.142
	Yes	1.17 (0.77, 1.78)	
	No	1.61 (1.13, 2.28)	
	Unknown	0.61 (0.21, 1.78)	
Baseline antiplatelet use			0.272
	Yes	1.69 (1.06, 2.70)	
	No	0.87 (0.44, 1.70)	
	Unknown	1.35 (0.94, 1.92)	
Baseline anti-thrombotic use			0.273
	Yes	1.27 (0.93, 1.73)	
	No	0.62 (0.16, 2.50)	
	Unknown	1.80 (1.09, 2.99)	
Baseline statin use			0.566
	Yes	1.19 (0.81, 1.76)	
	No	1.31 (0.80, 2.16)	
	Unknown	1.65 (1.02, 2.68)	
Baseline ACE/ARB use			0.734
	Yes	1.25 (0.76, 2.07)	
	No	1.68 (0.90, 3.13)	
	Unknown	1.32 (0.93, 1.86)	
Baseline beta-blocker use			0.126
	Yes	0.98 (0.59, 1.63)	
	No	2.22 (1.18, 4.17)	
	Unknown	1.32 (0.93, 1.86)	

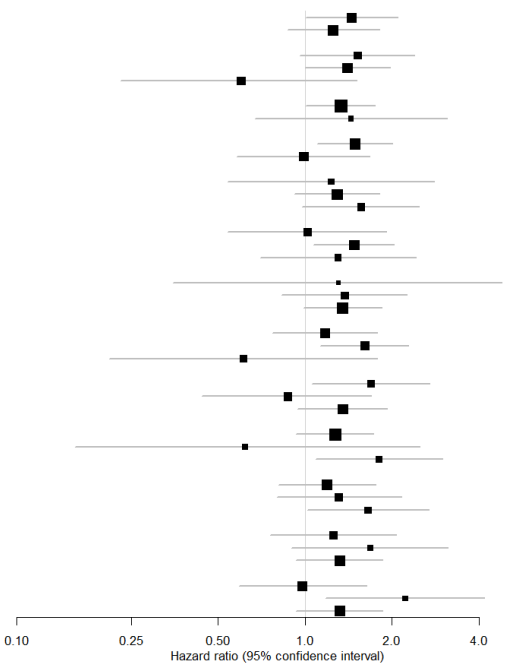
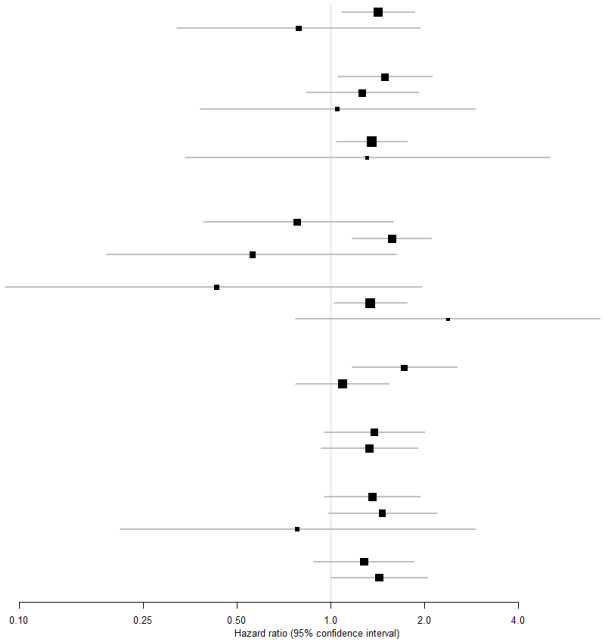


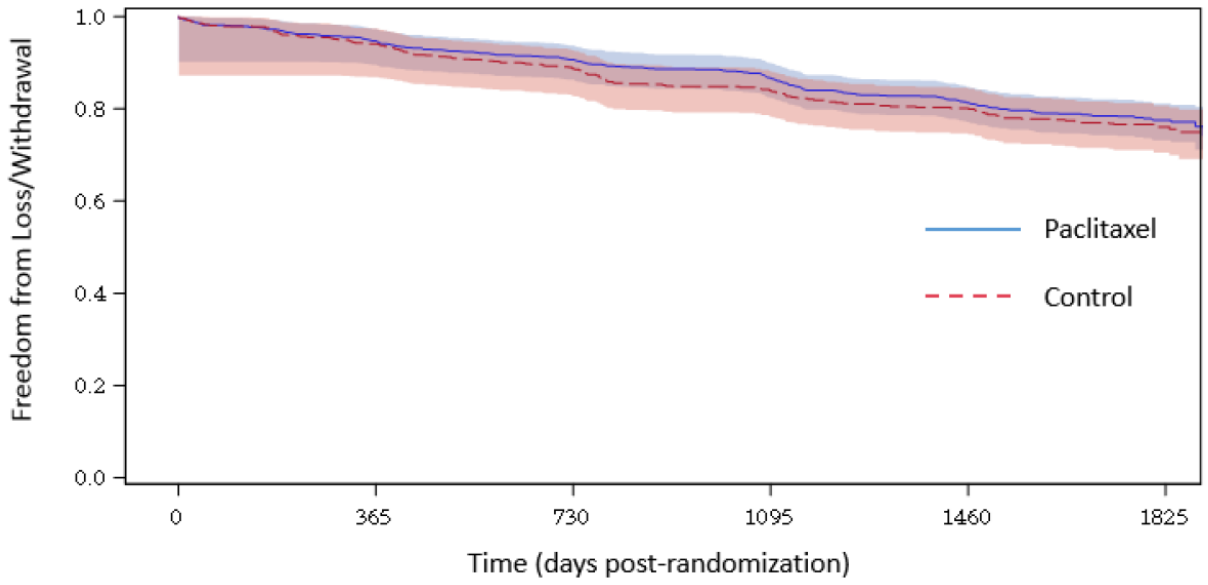
Figure S4 – Subgroup Results – Lesion Characteristics

		Hazard Ratio (95% CI)	Interaction P-value
Rutherford class			0.217
	3 or less	1.42 (1.08, 1.86)	
	> 3	0.79 (0.32, 1.93)	
	Unknown	NA	
Target Limb ABI			0.690
	Less than Median	1.49 (1.05, 2.12)	
	Median or Greater	1.26 (0.83, 1.91)	
	Unknown	1.05 (0.38, 2.90)	
Lesion Count			0.961
	1	1.35 (1.04, 1.76)	
	2	1.31 (0.34, 5.05)	
	Unknown	NA	
Target Lesion Type			0.111
	Restenotic and De novo	NA	
	Restenotic	0.78 (0.39, 1.59)	
	De novo	1.57 (1.17, 2.10)	
	Unknown	0.56 (0.19, 1.63)	
Lesion Location			0.200
	PPA/SFA	0.43 (0.09, 1.95)	
	SFA	1.34 (1.02, 1.76)	
	PPA	2.38 (0.77, 7.29)	
	Unknown	NA	
Lesion Length			0.079
	Less than Median	1.72 (1.17, 2.54)	
	Median or Greater	1.09 (0.77, 1.54)	
	Unknown	NA	
Stenosis			0.874
	Less than Median	1.38 (0.95, 2.00)	
	Median or Greater	1.33 (0.93, 1.90)	
	Unknown	NA	
Minimal lumen			0.578
	Less than Median	1.36 (0.95, 1.93)	
	Median or Greater	1.46 (0.98, 2.19)	
	Unknown	0.78 (0.21, 2.91)	
Vessel Diameter			0.625
	Less than Median	1.28 (0.88, 1.85)	
	Median or Greater	1.43 (1.00, 2.05)	
	Unknown	NA	



Subgroup results are from proportional hazards models with terms for subgroup, paclitaxel, and the interaction of subgroup and paclitaxel. P-values are from the test for the interaction term. Unknown refers to subjects where the subgroup defining variable was missing or not specified. NA = not applicable; not estimable due to a lack of events.

Figure S5 – Freedom From Loss-to-Follow-up/Withdrawal



References:

S1. Zhao Y, Herring AH, Zhou H, Ali MW, and Koch GW. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. Journal of Biopharmaceutical Statistics, 2014;24(2):229–2534.

S2. Fink S, Sensitivity Analyses for Informative Censoring in Time-to-Event Clinical Trials, 2015, https://epub.ub.uni-muenchen.de/25582/1/MA_FinkSimon.pdf.

VIVA Physicians

Patient-level Safety Meta-Analysis of PTX DES/DCB Trials

Statistical Analysis Plan

Version 2.0, 29JUL2019

Revision History

Revision Level	Effective Date	Description of Change
1	May 09 2019	Initial Release
2	July 29 2019	Addition of dose-response analysis, minor corrections

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used for the meta- analysis of patient level mortality data of paclitaxel (PTX) drug-eluting stent (DES)/drug-coated balloon (DCB) clinical trials.

2 Abbreviations

Abbreviation/Term	Definition
ABI	Ankle brachial index
DES	Drug-eluting stent
DCB	Drug-coated balloon
IPD	Individual participant data
LTF	Loss to follow-up
PTX	Paclitaxel
RCT	Randomized controlled trial
REML	Restricted maximum likelihood
SAP	Statistical analysis plan

3 Study Objectives

The primary purpose of this analysis is to perform a thorough individual participant (patient) data (IPD) meta-analysis of relevant randomized controlled trials to determine whether there is an effect of paclitaxel-coated balloons and stents on mortality in subjects with peripheral artery disease undergoing treatment for femoropopliteal disease.

The conclusions of a recent meta-analysis[1] indicate increased mortality at two- and five-years in patients following the use of paclitaxel-coated balloons and stents in the femoropopliteal artery. The conclusion of this meta-analysis has been noted by regulators who have also identified a potentially concerning signal of increased long-term mortality in study subjects treated with paclitaxel-coated products[2].

[1] Katsanos et al, "Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trial", JAHA, Vol 7, No. 24, December 2018.

[2] https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm633614.htm

Analyses will also seek to identify any possible confounding or treatment interactions with baseline variables, assess potential sources of bias, and better understand potential causes of any potential signal. These planned analyses could either confirm or refute the conclusions of the Katsanos (2018) meta-analysis, but more generally, IPD analyses are expected to provide unbiased and more precise estimates. Where applicable, the analysis will be conducted according to the guidelines outlined in the PRIMSA-IPD (Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data) Statement[3].

4 Study Data

4.1 Study Selection

4.1.1 Study Eligibility Criteria

De-identified patient-level data, including all-cause mortality, from clinical trials that meet the following criteria are available for analysis:

1. Randomized controlled trial (RCT) study of a paclitaxel-coated balloon / paclitaxel-eluting stent in the femoropopliteal artery against a non-drug eluting balloon or stent as control;
2. Patient population with peripheral artery disease of the femoral and/or popliteal artery and symptoms of intermittent claudication;
3. Clinical follow-up of at least 2 years available;
4. Commercially available devices in the United States as of 18 March 2019

4.1.2 Studies Included

The Katsanos meta-analysis included 12 studies at 2 years, and 3 studies at 4-5 years. Of the 12 at 2 years, 6 studies were eligible for our IPD meta-analysis while 6 studies were excluded from this meta- analysis as they were either not randomized trials of a PTX device against a PTA control (FINN-PTX), or were not studies of devices currently on the market in the US (THUNDER, FEMPAC, CONSEQUENT, ISAR- PEBIS, ACOART I).

Individual patient data were made available from the ILLUMENATE Pivotal (Phillips), the pivotal trial for US FDA approval, and Lutonix Japan (BD). These two trials were listed in the Katsanos paper as having a maximum of 1 year follow-up, but longer-term follow-up data were provided by the manufacturers.

Individual patient data were not available from other studies in the Katsanos paper that would have been eligible for this analysis with longer term follow-up (i.e., BATTLE and DEBELLUM).

Individual patient data were made available for the IMPERIAL study (Boston Scientific) but since both treatment arms were PTX devices, the study was excluded.

The following studies were identified as meeting the inclusion criteria with agreement to provide individual participant data:

[3] Stewart LA et al, "PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement" JAMA. 2015;313(16):1657-1665.

- ILLUMENATE Pivotal (Philips)
- ILLUMENATE EU-RCT (Philips)
- IN.PACT SFA (Medtronic)
- IN.PACT SFA Japan (Medtronic)
- Levant I (BD)
- Levant II (BD)
- Lutonix Japan (BD)
- Zilver PTX RCT (Cook)

All datasets will be provided directly to the NAMSA through a Data Sharing Agreement directly with each company providing data. VIVA Physicians will not be a party to the Data Sharing Agreements and will at no time have direct access to de-identified datasets. BD (previously BARD/Lutonix), Boston Scientific, Cook Medical, Medtronic, and Philips (previously Spectranetics), have agreed to provide their de- identified patient-level safety data via Data Sharing Agreements.

5 Sample Size

The sample size for this study is the sum of the number of patients randomized in the eight studies with IPD included in this meta-analysis. This sample size is not driven by power analyses but by the pre- defined sample size from each individual trial, and the data provided by each manufacturer.

6 Statistical Analyses

6.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) and R (version R 3.5.3 or later). The following R packages may also be used: survival package (version 3.4-4 or later), coxme package (version 2.2-10 or later) and metafor package (version 2.0-0 or later). Unless otherwise specified, an intent-to-treat approach (ITT) will be used with subjects analyzed according to their randomized assignment. Zilver PTX employed two randomizations; the first will be used for the primary analysis (the subsequent will be used as an additional sensitivity analysis). Forest plots will be used to summarize results by study and overall (as well as by subgroup). Kaplan-Meier analyses will employ Hall-Wellner 95% confidence bands.

6.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate.

6.1.2 Statistical Significance

Unless otherwise specified, a nominal 95% confidence level will be used. Any p-values will be assessed at the nominal two-sided 0.05 significance level. P-values will be rounded to three decimal places. If a p- value is less than 0.001 it will be reported as “<0.001”. If a p-value is greater than 0.999, it will be reported as “>0.999”.

6.1.3 Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places. For continuous parameters, means and medians will be reported to 1 additional decimal place than the measured value while standard deviation will be reported to 2 additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

6.2 Handling of Missing Data

For the primary analysis, missing data due to incomplete follow-up will be accounted for by assuming non-informative censoring with time-to-event analyses as described in Section 6.5. As a supplement to this analysis, a sensitivity analysis will be performed as described in Section 7.

6.3 Subject Disposition

The number of subjects in each analysis population will be presented along with reasons for any exclusions. The number of subjects will be summarized for each trial and overall. In addition, the number of subjects who completed each study or exited early will be summarized.

6.4 Baseline and Procedural Data

Descriptive statistics will be presented for clinically-relevant baseline demographic, medical history, procedural, and lesion characteristic variables. At a minimum, the variables described in section 6.5.3 will be evaluated, separately for each study and summarized across studies.

6.5 Analysis of Study Endpoints

6.5.1 Primary Outcome

The primary outcome of interest is all-cause mortality. Additional supportive analyses will be performed to evaluate the robustness of the results across varying statistical methodologies and subgroups.

The Katsanos meta-analysis based on aggregate results suggested a statistically significant effect of PTX on mortality; the purpose here is to further examine the prior finding. Accordingly, there are no formal pre-specified hypothesis tests associated with the primary outcome, rather a summary and characterization of the relative mortality risk in the two treatment arms will be provided through the analyses below.

6.5.1.1 Analysis Methods

The primary outcome of all-cause mortality will be summarized using a one-stage meta-analysis approach using the ITT analysis population. The measure of effect will be the hazard ratio of paclitaxel devices to control devices using a Cox proportional hazards model stratified by study. Stratifying the proportional hazards analysis by study will account for clustering of patients within study by specifying a separate baseline hazard function for each study.

To estimate the hazard ratio while accounting for potential study-to-study variation in the hazard ratio, the primary analysis model will include treatment arm as both a fixed effect and a random effect by study. The mathematical formulation based on Burke et al[4] is stated as:

$$h_{ij}(t) = h_{0i}(t)\exp\left(\theta_i x_{ij}\right)$$

$$\theta_i = \theta + u_i$$

$$u_i \sim N(0, \tau^2)$$

where $h_{ij}(t)$is the hazard rate over time (t) for participant *j* in trial *i*, and $h_{0i}(t)$ is the baseline hazard function in the i^{th} trial, θ_i denotes the treatment effect (log hazard ratio), and x_{ij} is an indicator variable for treatment (paclitaxel device vs. control), and u_i is the random study effect with variance τ^2.

Assessment of the proportional hazards assumption will be based on weighted residuals[5,6], utilizing a Kaplan-Meier transformation for the time scale, and will include a graphical assessment of time varying treatment effect. This will be performed based on data combined from all studies. If there is significant evidence the proportional hazards assumption does not hold, an extended Cox model approach will be employed, using a time varying coefficient for the treatment effect. In the presence of non-proportional hazards, these analyses will take primacy over the initial proportional hazards model. Specifically, a series of analyses will be performed where follow-up time is divided into epochs based on step functions. Splits will be made based on 6 month intervals (i.e. 0 to 6 months, 6 months to 12 months, etc.), 12 month intervals, and 18 month intervals. Intervals will be defined based on days, with 182.5 days serving as the cutpoint for 6 month intervals, 365 days serving as the cutpoint for 12 month intervals, and 547.5 days for 18 month intervals. For each split, the time limit for the last interval will extend to infinity and will be defined such that estimation is still possible for the last interval

Assessment of the proportional hazards assumption for the time varying coefficient models will be performed, again based on weighted residuals. Assessment of the proportional hazards assumption will also be performed separately for each study.Generally, for both the primary analysis and other relevant analyses, if there are issues with model fitting when using random effects (e.g., departures from proportional hazards, singular values, lack of convergence, etc.), alternative methods of accounting for study will be used (e.g., use of a fixed effect for study, or stratification by study, etc., depending on the particular analysis).

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[4] Burke D, et al, "Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ", Statistics In Medicine, 2017, 36, 855-875.

[5] Grambsch P, Therneau T, "Proportional hazards tests and diagnostics based on weighted residuals". Biometrika, 1994, 81, 515-26.

[6] Therneau T, Grambsch P, Modeling Survival Data: Extending the Cox Model, Springer, New York, 2000.

6.5.2 Secondary Analyses

Additional analyses using Kaplan-Meier methods will explore time to death. These will include separate curves for each study, examining treatment arm within study. For each, annual mortality estimates will be reported.

The primary analysis will be repeated based on only studies of DCB devices.

As a supportive analysis, a two-stage IPD meta-analysis will be performed. This entails first obtaining study-specific mortality hazard ratios, followed by combining the IPD hazard ratio estimates from all studies using random effects (via restricted maximum likelihood (REML)) aggregate meta-analysis. Heterogeneity will be assessed with the I2 statistic.

The primary analysis, using the Cox proportional hazards model, will be repeated in the As-Treated (AT) analysis population using the treatment that the patient received at the index procedure as the covariate of interest rather than the ITT arm designation.

The As-Treated analysis above will be repeated adjusting for baseline covariates.

All-cause mortality will be summarized by cause of death both overall, and by study, using frequencies and percentages. An analysis analogous to the primary analysis of all-cause mortality will be performed on each of the following outcomes (pending availability from each study) cardiovascular related deaths, pulmonary related deaths, infectious related deaths, cancer related deaths and "other" related deaths. Additionally, the Fine-Gray method of accounting for competing risk may be used if there are sufficient numbers of events by cause[7].

An assessment of treatment allocation over time will be performed for each study to ensure the balance of randomization throughout the study enrollment.

Due to the unique design characteristics of the Zilver PTX study, the primary analysis will be repeated using only the secondary randomization from the Zilver PTX study. That is, for this study, only subjects undergoing the secondary randomization (bare Zilver vs. Zilver PTX) will be included. These are subjects who were originally randomized to PTA and had suboptimal PTA outcomes.

The distribution crossing over (from control device to paclitaxel) will be summarized. This distribution will be summarized by study and overall across all studies. Cox proportional hazards models and Kaplan-Meier methods will be used to characterize any differences.

Cumulative incidence of PTX treatment over time will be summarized by treatment arm in order to understand exposure to PTX over time following the initial randomization and index procedure. Results will be summarized by study and overall across all studies.

[7] Therneau T, Grambsch P, Modeling Survival Data: Extending the Cox Model, Springer, New York, 2000.

A further assessment of loss to follow-up and/or withdrawal from the studies will also be made. This analysis will be done separately for each study and overall with all studies combined. As an additional characterization of loss to follow-up/withdrawal, Kaplan-Meier methods will be used to summarize the time to LTF/withdrawal between the treatment and control arms. This analysis will be in the form of a 'survival' graph estimating freedom from LTF/withdrawal for each study separately and all studies combined.

If the amount of crossover is considered a potential source of bias, the difference in mortality rates between the treatment and control arms will be reassessed assuming subjects who crossover are censored at the time of the crossover.

If loss to follow-up/withdrawal is considered a source of bias, then the following analysis will be completed on the ITT analysis population. First, a list of covariates will be defined that will be used to model the probability of censoring by logistic regression. The difference in mortality rate between the treatment and control arms will be estimated using a weighted Cox proportional hazards model where the weights are proportional to the inverse probability of censoring.

6.5.3 Additional Analyses

For descriptive purposes, summary statistics will be reported for clinically relevant baseline demographic, medical history, procedural, and lesion characteristic data. Data will be presented both overall and within treatment arm/by study. At a minimum, the following subject-level characteristics will be examined for differences across studies:

> age, sex, race, body mass index, smoking status, diabetes mellitus, coronary artery disease, hypertension, hyperlipidemia, renal insufficiency/eGFR, previous myocardial infarction, baseline medication use, Rutherford class (3 or less vs. greater than 3), target limb ABI, lesion count, lesion location, lesion length, % stenosis, minimal lumen, vessel diameter, and bail-out stenting.

Subjects from studies with missing values for a characteristic will be labeled as "unknown". As each randomized trial provides protection against confounding, no additional "post hoc" adjustment for baseline covariates is planned in line with guidelines[8].

[8] https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-adjustment-baseline-covariates_en.pdf

6.6 Subgroup Analyses

Subgroup analyses will be performed to further explore the difference in mortality between treatment arms. These analyses will assess treatment by covariate interactions. Initial analysis will examine treatment by covariate interactions in separate models (i.e. one model for each covariate). If significant interactions are found, additional exploratory work may examine higher order interactions. Subgroups of interest will be defined from baseline (pre-randomization) variables and may include (but are not limited to):

> age, sex, race, body mass index, smoking status, diabetes mellitus, coronary artery disease, hypertension, hyperlipidemia, renal insufficiency/eGFR, previous myocardial infarction, baseline medication use, Rutherford class (3 or less vs. greater than 3), target limb ABI, lesion count, lesion location, lesion length, % stenosis, minimal lumen, and vessel diameter.

Subjects with individually missing values, and subjects from studies with missing values for a characteristic (i.e. the variable is not available from the study) will be labeled as "unknown" and treated as an additional level of the subgroup. It is noted that interpretation of the "unknown" groups may be challenging due to confounding with study.

Mortality estimates will be calculated for these subgroups in an effort to understand if one group is contributing more to the overall mortality signal. Subgroups may need to be altered or dropped depending on the format of the data collected and available from each study. A p-value of 0.15 for an interaction term will be used as a general screening threshold to indicate potential variation in the treatment effect by subgroup, although the potential for a type I error is recognized.

Analyses will be performed overall for all studies, and separately by study.

7 Sensitivity Analysis

The primary analysis assumes non-informative censoring on the outcome of death for the ITT analysis population.

To assess impact of potentially informative censoring to change conclusions, a tipping point analysis will also be done[9,10]. This will use the primary analysis model, including as needed, extensions to the model for a time varying coefficient. Under an assumption of informative censoring, the mortality rate required in the censored subjects to change the conclusion of the

[9] Yue Zhao, Amy H. Herring, Haibo Zhou, Mirza W. Ali, and Gary W. Koch. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. Journal of Biopharmaceutical Statistics, 24(2):229–253, March 2014.

[10] Fink S, "Sensitivity Analyses for Informative Censoring in Time-to-Event Clinical Trials", 2015, https://epub.ub.uni-muenchen.de/25582/1/MA_FinkSimon.pdf.

primary analysis will be assessed (i.e., a p-value flipping from above/below 0.05 to below/above 0.05). Multiple imputation via Rubin's approach will be performed based on the following. Conditionally on the observed follow-up, events will be randomly imputed for censored subjects based on the treatment arm specific Kaplan-Meier survival distribution after the subject censoring time. A fixed power parameter will be applied to the Kaplan- Meier estimate (a value for delta greater than 1 implies a higher event rate among censored subjects than among observed, a value less than 1 implies a lower event rate). Through iteration, the value of delta that tips analyses between significant and non-significant results can be identified.

Any updated information on vital status (i.e., through additional efforts to determine long-term vital status beyond the original data collection for each study) will be incorporated in this tipping point analysis. These data are included as a sensitivity analysis rather than in the primary analysis because of potential differences in the data collection and evaluation process between data originally collected in the studies and subsequent efforts to obtain vital status.

8 Dose Response Analysis

An exploratory analysis examining a potential dose response relation will be performed. Since paclitaxel dose is not randomized, this analysis will employ an "as-treated" approach, using the actual treatment received at the index procedure. Additionally, covariate adjustment will be performed via propensity score methods. As in the primary analysis, mortality will be examined via a proportional hazards model.

Dose for each individual will be based on the nominal device dose at the index procedure. While paclitaxel exposure over time is of interest, there are limitations with regards to both available data (post-index paclitaxel exposure was not consistently collected in trials over time) and the ability to perform covariate adjustment without introducing bias. Therefore, as with other analyses, focus will be on the index procedure.

Control subjects will be included in the analysis; those without paclitaxel exposure will be included with a dose of zero. Dose will be included as a main effect in the proportional hazards model, based on within-study tertile of dose and zero dose (for four groups). Two-sided 95% confidence intervals will be used to summarize findings and tests will be performed for the overall effect of dose.

Additional parameterizations for dose will be used in sensitivity analyses to further explore the relation between dose and mortality. These will include:

- Dose as a continuous linear variable
- Dose as a continuous flexible variable (i.e. a spline fit)

We will also fit models examining a dose by study interaction. Evidence of heterogeneity will be explored with random effects models. The proportional hazards assumption will be assessed.

Covariate adjustment via propensity score (inverse probability of treatment weighting) will be used to attempt to address potential differences between dose groups using generalized logits to handle multiple exposure groups. The choice of covariates for adjustment is challenging due to multiple issues, including the potential sparsity of covariates over the dose by study groups, distribution of covariates with very high or very low prevalence (again leading to sparsity issues), and complications related to causal inference and the potential to inadvertently introduce bias[11]. In particular, lesion characteristics may be a potential instrumental variable (a cause of the dose exposure, but with no relation to mortality other than through dose) and so they are omitted from the primary covariate adjustment for dose analyses.

Accordingly, the primary list of covariates for dose analyses is drawn from the previously specified listed of baseline subgroups but will be restricted to:

age, sex, race, body mass index, smoking status, diabetes mellitus, coronary artery disease, hypertension, hyperlipidemia, renal insufficiency/eGFR, previous myocardial infarction, Rutherford class (3 or less vs. greater than 3), target limb ABI.

Additional sensitivity analyses will attempt to also adjust for lesion characteristics (lesion count, lesion location, lesion length, % stenosis, minimal lumen, and vessel diameter) or baseline medication use.

The distribution of covariates between dose groups will be examined.

Updated information on vital status, as discussed in Section **Error! Reference source not found.**, will be incorporated as a sensitivity analysis to the dose response analysis (i.e. the primary dose response analysis will use the original mortality results as in the overall primary analysis).

9 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

[11] VanderWeele T, Principles of confounder selection. Eur J Epidemiol. 34(3):211-219, 2019.