17 Secondary endpoints

Within the following chapters, the results of the analyses of secondary endpoints are presented.

17.1 Time to event endpoints

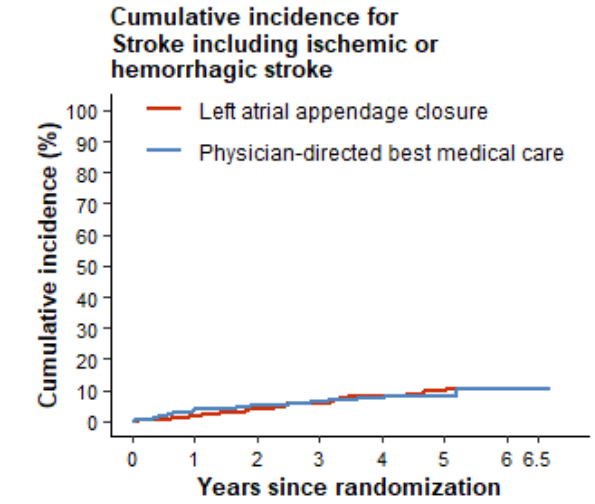
The following table shows the results of secondary time-to-event endpoints using the Cox proportional hazards models in the ITT population as described in the SAP including:

- Number of events
- Incidences per patient-years
- Hazard ratio with 95% confidence interval (adjusted for center using strata)
- p-values for a two-sided test for difference
- the number of individuals included in the analysis

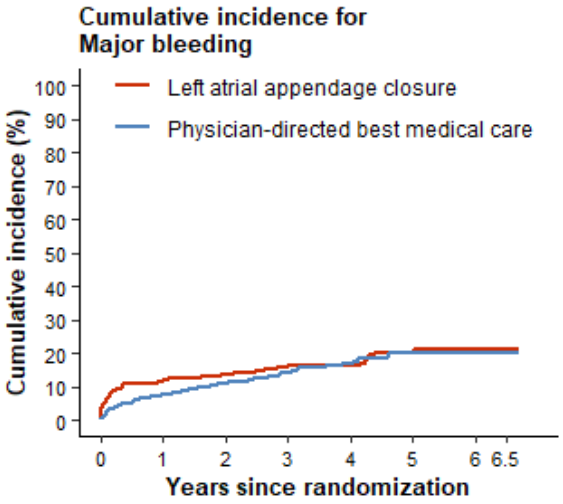
Table 03: Results of the analysis of secondary time to event endpoints

	Left atrial appendage closure	**Physician-directed best medical care**	**Left atrial appendage closure vs. Physician-directed best medical care**		
Endpoint	**Events/ patient-years (incidence per 100 patient-years)**	**Events/ patient-years (incidence per 100 patient-years)**	**Adjusted hazard ratio (95% CI)**	**p-value**	**N**
Primary endpoint	155/920.8 (16.83)	127/957.0 (13.27)	1.28 (1.01, 1.62)	0.0419	888
Systemic embolism	3/1042.7 (0.29)	1/1045.4 (0.10)	2.99 (0.31, 28.79)	0.3425	888
Stroke including ischemic or hemorrhagic stroke	27/1019.0 (2.65)	27/1015.1 (2.66)	1.02 (0.59, 1.74)	0.9549	888
Major bleeding	70/941.5 (7.43)	61/978.7 (6.23)	1.21 (0.86, 1.71)	0.2811	888
Cardiovascular or unexplained death	99/1045.2 (9.47)	81/1045.4 (7.75)	1.25 (0.93, 1.68)	0.1402	888
All-cause death	155/1045.2 (14.83)	141/1045.4 (13.49)	1.12 (0.89, 1.40)	0.3484	888
Myocardial infarction	14/1021.8 (1.37)	20/1016.9 (1.97)	0.68 (0.34, 1.35)	0.2720	888
TIA	9/1029.1 (0.87)	10/1028.6 (0.97)	0.88 (0.36, 2.17)	0.7800	888
Ischemic stroke	18/1022.8 (1.76)	15/1022.8 (1.47)	1.17 (0.59, 2.33)	0.6500	888
Hemorrhagic stroke	10/1039.5 (0.96)	13/1037.4 (1.25)	0.83 (0.36, 1.90)	0.6611	888
Ischemic stroke or Systemic embolism	20/1020.3 (1.96)	16/1022.8 (1.56)	1.23 (0.63, 2.37)	0.5440	888
Hemorrhagic stroke or Systemic embolism	13/1037.1 (1.25)	14/1037.3 (1.35)	0.99 (0.46, 2.12)	0.9853	888
Stroke or Systemic embolism	29/1016.5 (2.85)	28/1015.0 (2.76)	1.05 (0.63, 1.77)	0.8471	888
Hospitalization for bleeding or cardiovascular event	284/535.9 (53.00)	250/633.9 (39.44)	1.27 (1.07, 1.50)	0.0070	888
MACCE	92/994.1 (9.25)	81/988.6 (8.19)	1.15 (0.85, 1.55)	0.3739	888

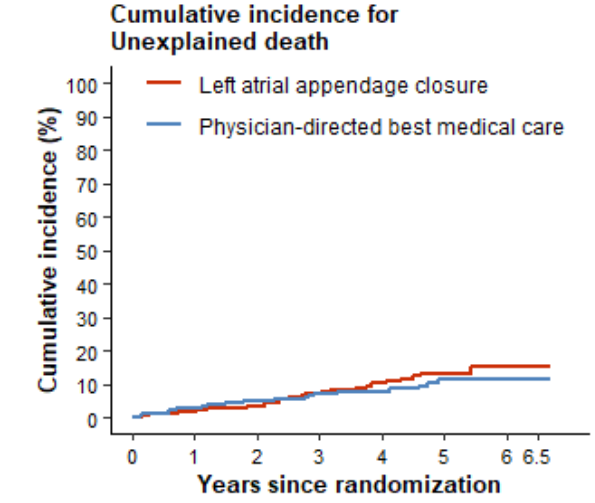
The cumulative incidences estimated with the Aalen-Johansen estimator to account for competing events are shown in the following figures.



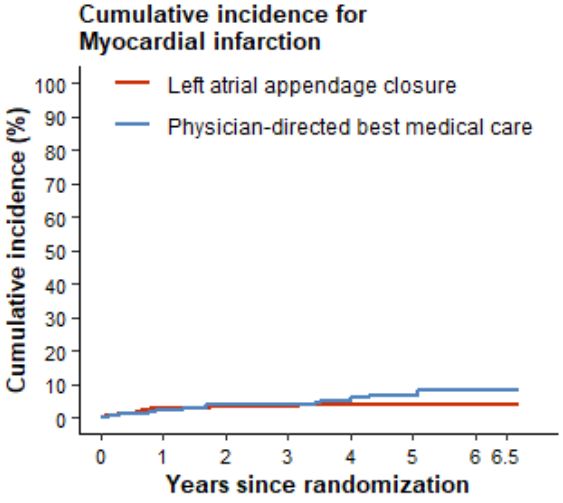
Number at risk							
PD-BMC	442	321	218	149	84	43	7
LAAC	446	331	225	135	81	39	11



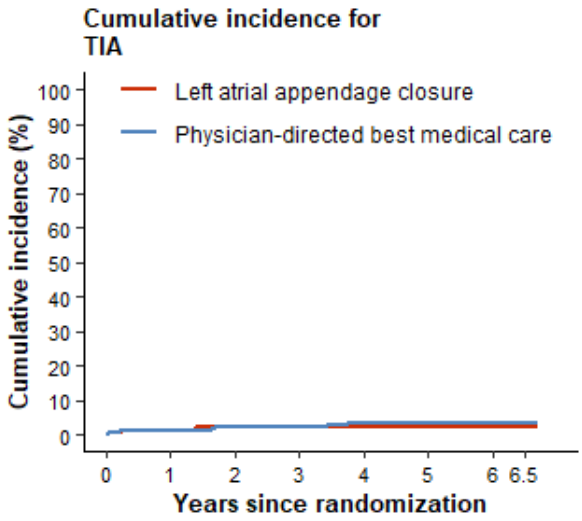
Number at risk							
PD-BMC	442	311	209	139	80	42	8
LAAC	446	305	209	122	76	34	9



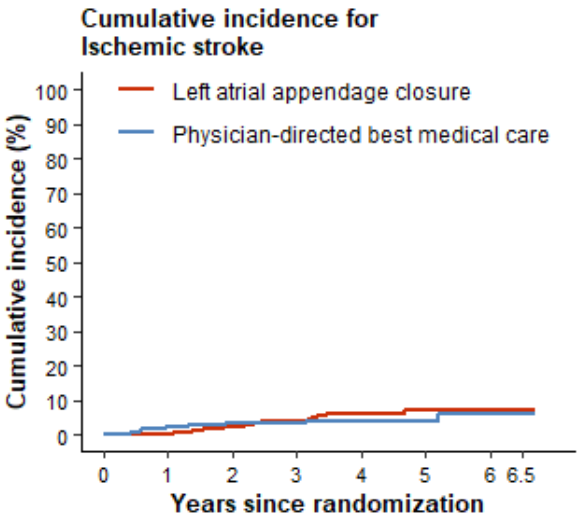
Number at risk							
PD-BMC	442	328	227	154	87	47	8
LAAC	446	333	232	141	87	41	11



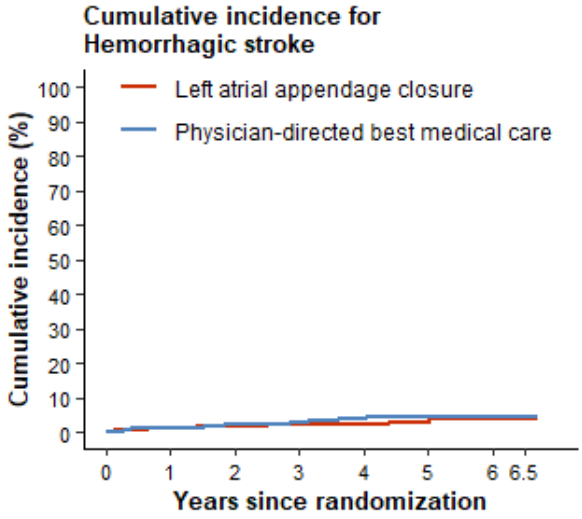
Number at risk							
PD-BMC	442	321	219	149	83	43	7
LAAC	446	323	226	137	84	41	11



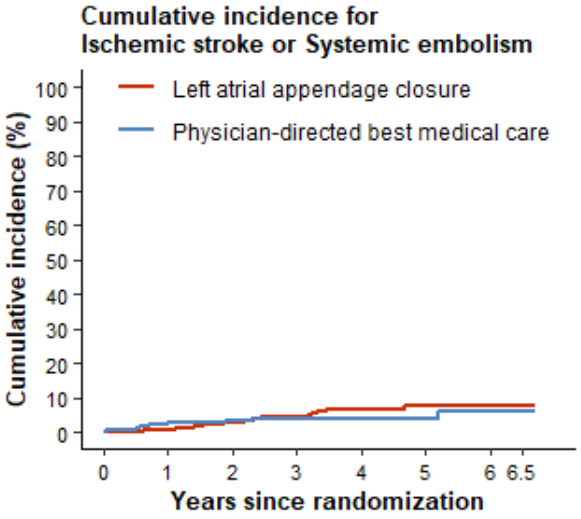
Number at risk							
PD-BMC	442	325	223	150	84	46	8
LAAC	446	329	228	138	84	40	11



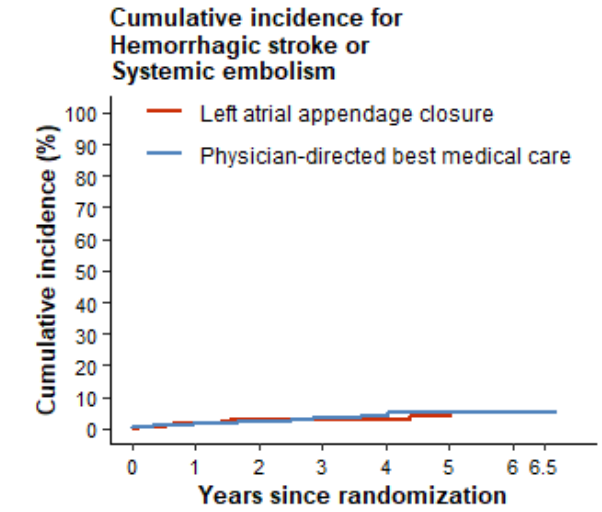
Number at risk							
PD-BMC	442	323	220	151	84	44	7
LAAC	446	333	226	135	81	40	11



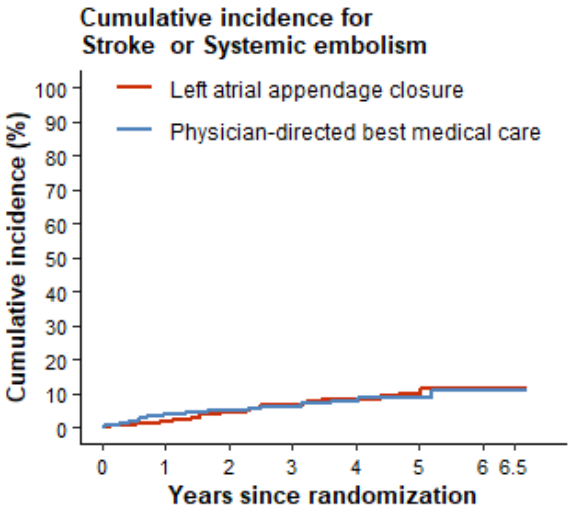
Number at risk							
PD-BMC	442	326	224	152	87	46	8
LAAC	446	331	230	140	87	40	11



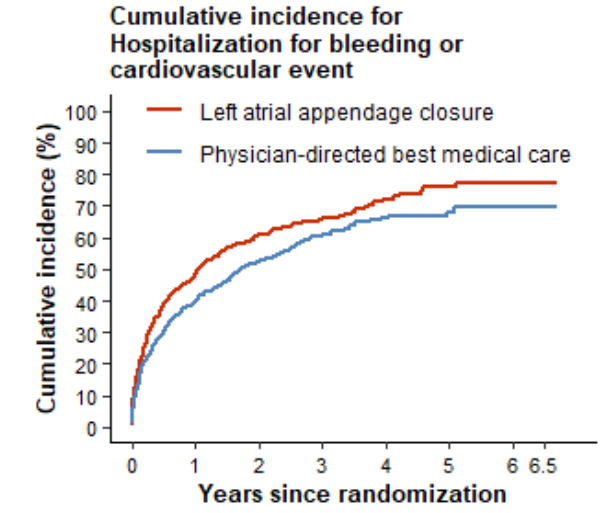
Number at risk							
PD-BMC	442	323	220	151	84	44	7
LAAC	446	332	224	135	81	40	11



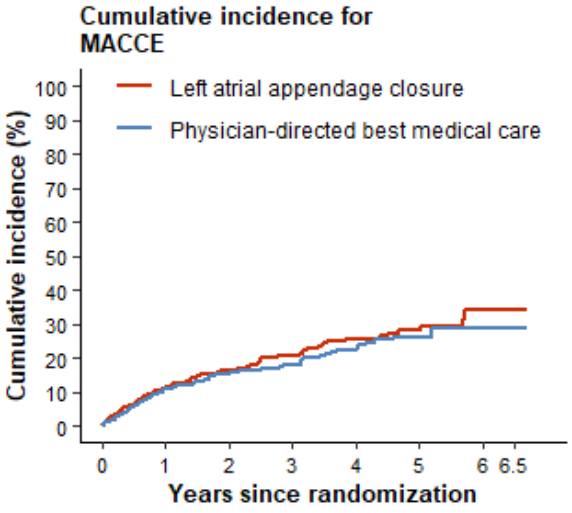
Number at risk							
PD-BMC	442	326	224	152	87	46	8
LAAC	446	330	228	140	87	40	11



Number at risk							
PD-BMC	442	321	218	149	84	43	7
LAAC	446	330	223	135	81	39	11



Number at risk							
PD-BMC	442	215	126	68	36	17	3
LAAC	446	184	100	55	30	11	1



Number at risk							
PD-BMC	442	314	211	144	80	39	7
LAAC	446	320	217	131	79	39	11

The result of Kaplan-Meier estimation is shown in the following figure.

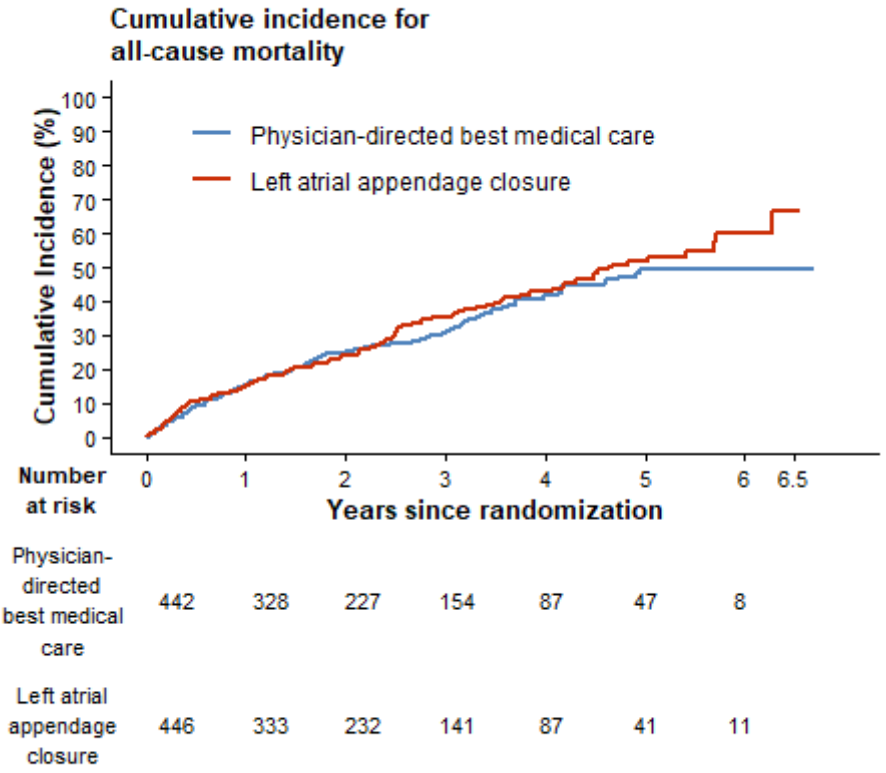


Figure 07: Kaplan Meier plot for secondary endpoint all-cause death

The following plots are shown to check the proportional hazards assumption.

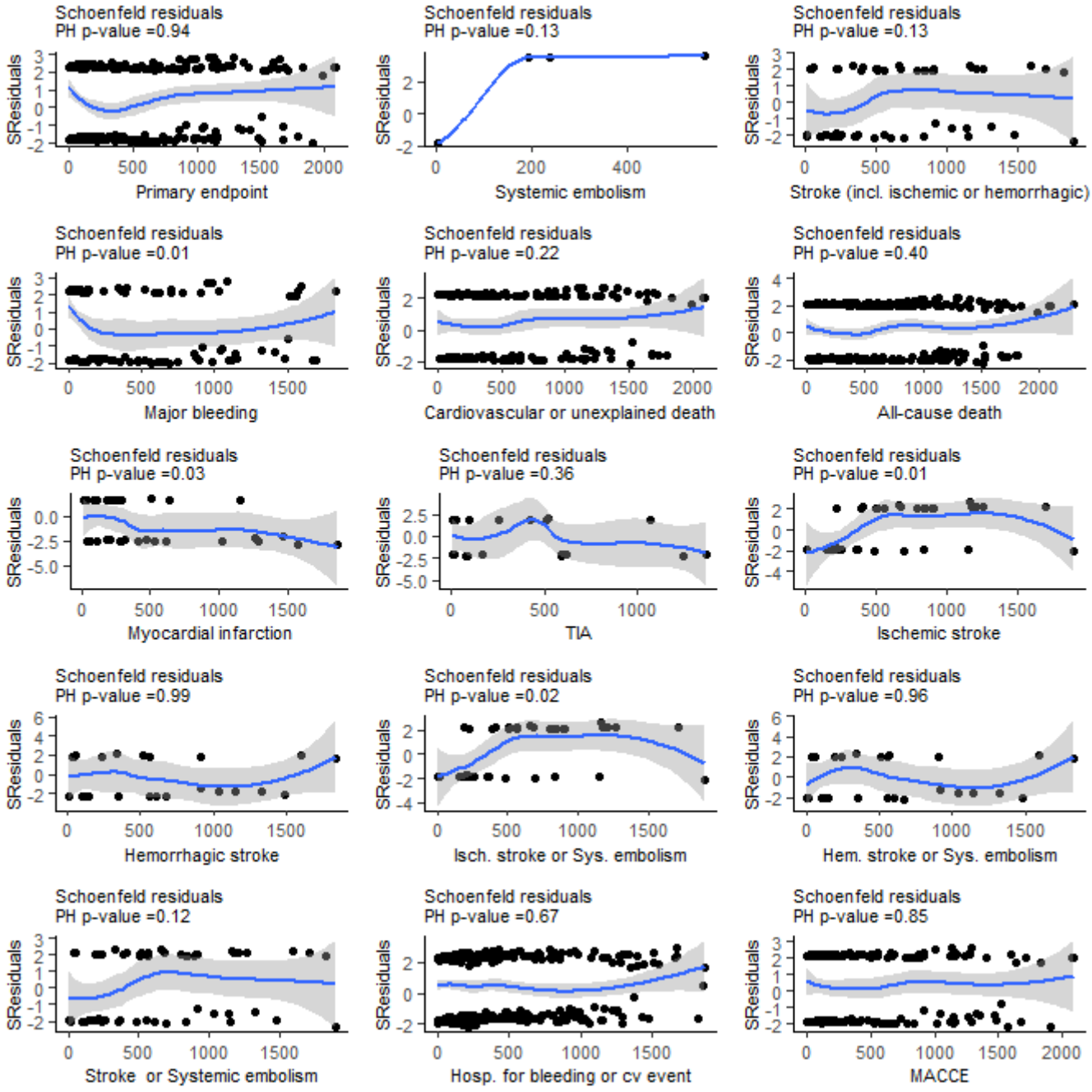


Figure 08: Check PH assumption Secondary Endpoints (Schoenfeld)

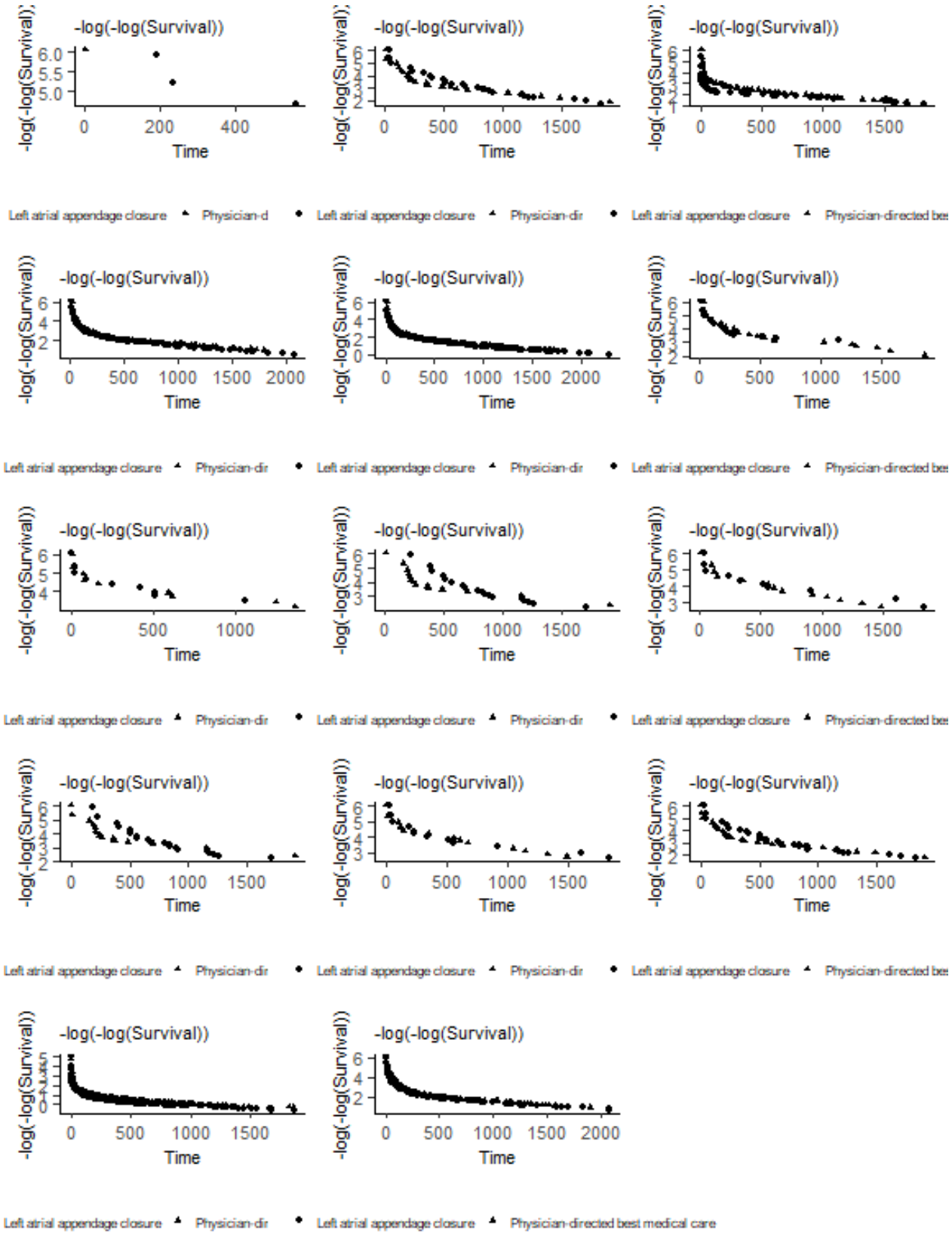


Figure 09: Check PH assumption Secondary Endpoints (-log-log Survival)

18 Safety analysis

The following tables show the frequencies for the safety endpoints and number of SAEs as described in the SAP using the Evaluated for Safety (EFS) population.

Definition of successes:

- Device success: The device is deployed stable
- Technical success: Device success + no peri-device leak >5mm + no device related embolisation within implantation + no death within implantation
- Procedural success: Technical success + no pericardial tamponade within 7 days + no death within 7 days

18.1 Safety endpoints

Outcome	Intervention N=446
Patients with LAAO implantation	421/446 (94.39%)
Device-related complications until day 7 or discharge	
Device-related thrombus	0/421 (0%)
Pericardial effusion	11/421 (2.61%)
Leaks	20/421 (4.75%)
<3mm	16/421 (3.8%)
3-5mm	1/421 (0.24%)
>5mm	3/421 (0.71%)
Pericardial tamponade procedure-related death	0/421 (0%)
Technical and procedural success of device implantation	
Device success (device deployed stable)	414/421 (98.34%)
Technical success (device implanted in correct positon with a peri-device leak <=5mm and no device-related complications (embolisation/death) within implantation)	411/421 (97.62%)
Procedural success (technical success with no procedure-related complications (pericardial tamponade/death) within 7 days)	406/421 (96.44%)
Peri-procedural outcomes until day 7 or discharge	
Pericardial tamponade	5/421 (1.19%)
Treated with pericadiocentesis	4/421 (0.95%)
Treated surgically	1/421 (0.24%)
Resulted in death	0/421 (0%)
Pericardial effusion	11/421 (2.61%)
Major bleeding requiring transfusion (BARC 3-5)	18/421 (4.28%)

Outcome	Intervention N=446
Non-procedural major bleeding (after 7 days)	49/421 (11.64%)
Pulmonary embolism	0/421 (0%)
Air embolism	0/421 (0%)
Device embolization	1/421 (0.24%)
Removed percutaneously	0/421 (0%)
Removed surgically	1/421 (0.24%)
Procedure related stroke	1/421 (0.24%)
Procedure related TIA	1/421 (0.24%)
Peripheral embolism	1/421 (0.24%)
Systemic infection	2/421 (0.48%)
Death	2/421 (0.48%)
Total patient with at least one peri-procedural complication	28
Peri-procedural outcomes until day 30	
Pericardial tamponade	5/421 (1.19%)
Treated with pericadiocentesis	4/421 (0.95%)
Treated surgically	1/421 (0.24%)
Resulted in death	0/421 (0%)
Pericardial effusion	12/421 (2.85%)
Major bleeding requiring transfusion (BARC 3-5)	25/421 (5.94%)
Pulmonary embolism	0/421 (0%)
Air embolism	0/421 (0%)
Device embolization	1/421 (0.24%)
Removed percutaneously	0/421 (0%)
Removed surgically	1/421 (0.24%)
Procedure related stroke	1/421 (0.24%)
Procedure related TIA	1/421 (0.24%)
Peripheral embolism	1/421 (0.24%)
Systemic infection	2/421 (0.48%)
Death	4/421 (0.95%)

Outcome	Intervention N=446
Total patient with at least one peri-procedural complication	36

Table 04: Deaths by group

	Physician-directed best medical care	Left atrial appendage closure	Total
Death within 7 Days			
no	442/442 (100.0%)	445/446 (99.8%)	887/888 (99.9%)
yes	0/442 (0.0%)	1/446 (0.2%)	1/888 (0.1%)
Death within 30 Days			
no	436/442 (98.6%)	441/446 (98.9%)	877/888 (98.8%)
yes	6/442 (1.4%)	5/446 (1.1%)	11/888 (1.2%)