Supplementary Online Content

Nogueira RG, Frei D, Kirmani JF, et al; Penumbra Separator 3D Investigators. Safety and efficacy of a 3-dimensional stent retriever with aspiration-based thrombectomy vs aspiration-based thrombectomy alone in acute ischemic stroke intervention: a randomized clinical trial. *JAMA Neurol*. Published online January 2, 2018. doi:10.1001/jamaneurol.2017.3967

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Exclusion Criteria, Device Use, and Statistical Analysis

Clinical Events Committee

A Clinical Events Committee (CEC) reviewed and adjudicated for severity and causality (disease-, procedure-, or device-relatedness), primary safety endpoint events, intracranial hemorrhages (ICH), deaths, neurological serious adverse events (SAEs), all strokes and select other events that occurred over the course of the study. The CEC adjudicated data superseded the investigator-reported data in all analyses of adverse events.

Study Exclusion Criteria:

- History of stroke in the past 3 months
- Females who are pregnant
- Pre-existing neurological or psychiatric disease that could confound the study results such as a pre-stroke mRS score $\geq$1
- Known severe allergy to contrast media
- Uncontrolled hypertension (defined as systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg)
- CT evidence of the following conditions at randomization:
  - .1.1.1 Significant mass effect with midline shift
  - Large infarct region >1/3 of the middle cerebral artery territory
  - Evidence of intracranial hemorrhage
- Angiographic evidence of an arterial stenosis proximal to the occlusion that could prevent thrombus removal
- Angiographic evidence of preexisting arterial injury
- Rapidly improving neurological status prior to enrollment
- Bilateral stroke
- Intracranial tumors
- Known history of cerebral aneurysm or arteriovenous malformation
- Known hemorrhagic diathesis, coagulation deficiency, or on anticoagulant therapy with an International Normalized Ratio (INR) of >1.7
- Baseline platelets <50,000
- Use of IV heparin in the past 48 hours with PTT >1.5 times the normalized ratio
- Baseline glucose <50mg/dL or >300mg/dL
- Life expectancy less than 90 days prior to stroke onset
- Participation in another clinical investigation that could confound the evaluation of the study device

Device Use

The 3D was employed in 88 participants in the 3D/PS group and in 0 participants in the PS group. A Separator device was used in 10 participants in the 3D/PS group and in 65 participants in the PS group. An adjunctive device was employed in 8 participants in the

3D/PS group and in 21 participants in the PS group. A single pass of the 3D was employed in 30% of participants in the 3D/PS group, and the mean number of passes was 2.6 ± 1.5. ADAPT was employed in 35 participants in the PS group.

Statistical Analysis Plan

A Statistical Analysis Plan is included with the Protocol, in an independent file.

Per Protocol and Intent to Treat Population Criteria

The Intent to Treat (ITT) population included all randomized patients.
The Per Protocol (PP) population included patients who met inclusion/exclusion criteria, received the assigned treatment, and did not have major protocol deviations. The following 25 patients (11 3D/PS, 14 PS) were excluded from the per protocol analysis: no attempt to treat with the Penumbra System (n=8; 4 3D/PS, 4 PS); mRS inclusion criteria not met (n=2; 1 3D/PS, 1 PS); vessel size or location inclusion not met (n=7; 3 3D/PS, 4 PS); cerebral aneurysm exclusion met (n=1; PS); inability to access occlusion (n=4; 1 3D/PS, 3 PS); stenting required for dissection or stenosis prior to treatment (n=2; 1 3D/PS, 1 PS); resolution of clot prior to treatment (n=1; 3D/PS).

Non-inferiority Margin

The trial design, selection of the primary endpoints, and use of the Per Protocol population for the primary analysis were results from discussions with the US Food and Drug Administration which predated the recent positive RCTs and the consensus for mTICI 2b-3 as the generally accepted reperfusion endpoint. Active control trials using a non-inferiority design to demonstrate the safety and effectiveness of a novel medical device are commonly implemented when clinical equipoise is lacking for the inclusion of a non-treatment control arm, as it was previously seen in the SWIFT and TREVO 2 trials.[1,2] As stated earlier, results from the recent RCTs have firmly established that, in this stroke cohort with proximal large vessel occlusion, a non-treatment control arm without mechanical thrombectomy is no longer tenable, thus an active control design is the only ethical choice. Another key criterion for a design of this nature is that the active control must show "assay sensitive" i.e., there is clear evidence that the control device demonstrated a treatment effect based on historical control data.[3] Moreover, the treatment size must be greater than the margin selected for non-inferiority for this study (15%) or the conclusion is not considered valid. The results on revascularization for this study clearly indicate that criterion was also met. The primary endpoint (mTICI 2-3 reperfusion) was achieved in 82.3% of the control (PS) patients with 69.8% of them achieving mTICI 2b-3 reperfusion. A review of the literature revealed that the rate of spontaneous revascularization in patients with confirmed large vessel occlusion is less than 20%.[4,5] This is in concordance with the results of the PROACT-II trial, which remains the only prospective randomized study without any active reperfusion therapy in the control arm. In PROACT-II, only 18% of the controlled patients had spontaneously revascularized on follow-up imaging.[6] In the ESCAPE, MR CLEAN, and SWIFT PRIME trials, 78.7%, 90.6%, and 100% of the respective control patients received intravenous t-PA. Reperfusion on follow-up imaging was seen in 31.2%, 32.9%, and 40% of these patients, respectively.[7-9] This would indicate a treatment difference of approximately 35% with the most conservative estimate, far exceeding the margin for non-inferiority of 15%,

which minimizes the risk for a type 1 error. Thus, use of the PS as the active control with a 15% non-inferiority margin on the rate of revascularization in this study was in fact an appropriate choice.

The selection of mTICI of 2-3 as the marker for successful recanalization, while not consistent with the currently accepted benchmark of mTICI 2b-3, was selected due to the historical precedence set by the other pivotal trials for a similar indication.[1,2,10,11] Regardless, a review of the mTICI 2b-3 results showed the difference in definitions did not materially affect the conclusion of this study (Table 2). The use of the PP as versus the Intent To Treat population for the primary analysis of effectiveness in a non-inferiority trial is controversial.[12-15] Proponents of the PP approach believe that the ITT analysis is most appropriate for a superiority but not non-inferiority trial because ignoring protocol violations or poorly executed protocols would surely bias in favor of finding two treatment modalities to appear similar. The counter to this argument is that data is lacking to clearly demonstrate this is a valid assumption. For this study, we have found that the ITT analysis was supportive of the PP analysis in that both methods concluded that the 3D/PS is non-inferior to the PS.

eTable 1. Types of Device-Related Adverse Events (Intention to Treat)

A total of 13 serious adverse events within 24 hours of the procedure for 9 patients were adjudicated by the CEC as device related.

Adverse Event Description	All Patients (N=13)	3D / Penumbra System (N=4)	Penumbra System (N=9)
Blood transfusion	2	1	1
Vessel perforation/ dissection	2	1	1
Haemorrhage intracranial	1	1	0
Intubation	2	0	2
Ischaemic cerebral infarction*	1	0	1
Stroke in evolution**	2	0	2
Vessel re-occlusion	3	1	2

Other events of interest: Based on Core Lab adjudication, distal emboli occurred in 3 patients, 1 in the 3D/PS arm (ITT 1.0%; target vessel left MCA M1, new distal embolus in distal left ACA) and 2 in the PS arm (ITT 2.0%; target vessel left MCA M1, distal embolus in ACA A2 and target vessel left ICA supraclinoid, distal embolus in left ACA).

*Ischaemic cerebral infarction is defined as 'new ischemic infarct" as adjudicated by CEC.
**Stroke in evolution is defined as progression of index stroke with neurological worsening.

eTable 2. Baseline Patient Characteristics and Process Times (Per Protocol)

	All Patients (n=173)	3D/Penumbra System (n=87)	Penumbra System (n=86)
Age (years), mean (SD)	66.9 (12.9)	67.9 (13.0)	65.9 (12.7)
Female, %	56.1% (97/173)	59.8% (52/87)	52.3% (45/86)
Baseline NIHSS, median [IQR]	18 [14, 22]	18 [14, 21]	18 [14, 24]
Baseline NIHSS ≥ 20, %	39.3% (68/173)	35.6% (31/87)	43.0% (37/86)
Baseline ASPECTS, median [IQR]	8 [7, 9]	8 [6.5,9]	8 [7,9]
Admission systolic BP mmHg, mean (SD)	142.1 (20.3)	142.7 (20.1)	141.4 (20.5)

Pre stroke modified Rankin scale score, %			
- 0	97.7% (169/173)	97.7% (85/87)	97.7% (84/86)
- 1	2.3% (4/173)	2.3% (2/87)	2.3% (2/86)
Hypertension, %	77.5% (134/173)	75.9% (66/87)	79.1% (68/86)
Admission glucose (mg/dL), median [IQR]	119.0 [103.0,145.0]	121.5 [101.0,144.5]	118.0 [103.0,145.0]
Diabetes, %	26.0% (45/173)	25.3% (22/87)	26.7% (23/86)
Atrial fibrillation, %	48.0% (83/173)	54.0% (47/87)	41.9% (36/86)
Site of primary occlusion (Core Lab), %:			
ICA	19.1% (33/173)	14.9% (13/87)	23.3% (20/86)
MCA M1	67.6% (117/173)	71.3% (62/87)	64.0% (55/86)
MCA M2	12.1% (21/173)	13.8% (12/87)	10.5% (9/86)
PCA	0.6% (1/173)	0% (0/87)	1.2% (1/86)
Basilar	0.6% (1/173)	0% (0/87)	1.2% (1/86)
Left hemisphere occlusion, %	50·.9% (88/173)	40.2% (35/87)	61.6% (53/86)
Stenosis proximal to the primary occlusion, %	6.9% (12/173)	4.6% (4/87)	9.3% (8/86)
Pre treatment mTICI 0 or 1, %	94.8% (164/173)	93.1% (81/87)	96.5% (83/86)
Treatment with IV tPA, %	65.9% (114/173)	65.5% (57/87)	66.3% (57/86)
Time from symptom onset to IV rtPA (hr), median [IQR]	101.0 [84.0,136.0]	103.0 [83.0,136.0]	99.0 [85.0,135.0]
Time from onset to ED arrival, minutes, median [IQR]	110.0 [47.0,226.0]	113.0 [45.0,207.0]	98.5 [48.0,235.0]
Time from ED arrival to CT, minutes, median [IQR]	16.0 [11.0, 29.0]	16.0 [11.0,29.0]	15.0 [10.0,29.0]
Time from CT to arterial puncture, minutes, median [IQR]	93.0 [56.0,128.0]	93.5 [53.0,134.0]	92.0 [57.0,128.0]
Time from puncture to mTICI 2-3	47.0 [32.0, 72.0]	49.0 [33.0,74.0]	42.5 [28.0,67.0]

reperfusion, minutes, median [IQR]			
Time from puncture to mTICI 2b-3 reperfusion, minutes, median [IQR]	44.0 [29.0, 70.0]	49.0 [33.0,74.0]	39.0 [25.0,61.5]

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; MCA, middle cerebral artery; M1, main MCA stem; M2, second-order MCA branch; M3, third-order MCA branch

eTable 3. Primary Outcomes (Per Protocol)

	All Patients (n=173)	**3D/PS (n=87)**	**PS (n=86)**	**Difference (90% CI)**
mTICI 2-3	87.3% (151/173)	88.5% (77/87)	86.0% (74/86)	2.5% (-5.9%, 10.8%)
mTICI 2b-3	79.2% (137/173)	83.9% (73/87)	74.4% (64/86)	9.5% (-0.6%, 19.6%)

eTable 4. Safety and Secondary Outcomes (Per Protocol)

	All Patients (n=173)	**3D/Penumbra System (n=87)**	**Penumbra System (n=86)**
Device-related SAE (24 hours)	4.6% (8/173)	4.6% (4/87)	4.7% (4/86)
Procedure-related SAE (24 hours)	12.1% (21/173)	10.3% (9/87)	14.0% (12/86)
All-cause mortality at 90 days	23.1% (40/173)	21.8% (19/87)	24.4% (21/86)
Symptomatic ICH within 24 hours	3.5% (6/173)	3.4% (3/87)	3.5% (3/86)
Good clinical outcome at 30 days post-procedure	57.8% (100/173)	58.6% (51/87)	57.0% (49/86)
90-day mRS 0-2	45.0% (72/160)	41.6% (32/77)	48.2% (40/83)
Good neurological outcome at 90 days post-	60.6% (97/160)	61.0% (47/77)	60.2% (50/83)

procedure			

eTable 5. Definition and Distribution of mTICI Scores (Intention to Treat)

mTICI Baseline	All Patients (n=198)	3D / Penumbra System (N=98)	Penumbra System (N=100)
0 (**No Perfusion**. No antegrade flow beyond the point of occlusion.) - % (n/N)	84.8% (167 / 197)	83.7% (82 / 98)	85.9% (85 / 99)
1 (**Penetration With Minimal Perfusion**. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.) - % (n/N)	9.1% (18 / 197)	7.1% (7 / 98)	11.1% (11 / 99)
2a (Partial filling with <50% of the entire vascular territory is visualized.) - % (n/N)	5.1% (10 / 197)	7.1% (7 / 98)	3.0% (3 / 99)
2b (**Partial filling** with ≥50% of the entire vascular territory is visualized. If complete filling of all of the expected vascular territory is visualized, the filling is slower than normal.) - % (n/N)	0.5% (1 / 197)	1.0% (1 / 98)	0.0% (0 / 99)
3 (**Complete Perfusion**. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.) - % (n/N)	0.5% (1 / 197)	1.0% (1 / 98)	0.0% (0 / 99)

mTICI After Penumbra Treatment	All Patients (n=198)	3D / Penumbra System (N=98)	Penumbra System (N=100)
0 (**No Perfusion**.) - % (n/N)	11.1% (21 / 190)	10.6% (10 / 94)	11.5% (11 / 96)
1 (**Penetration With Minimal Perfusion**.) - % (n/N)	4.2% (8 / 190)	2.1% (2 / 94)	6.3% (6 / 96)
2a (Partial filling.) - % (n/N)	8.9% (17 / 190)	5.3% (5 / 94)	12.5% (12 / 96)
2b (**Partial filling**) - % (n/N)	28.4% (54 / 190)	26.6% (25 / 94)	30.2% (29 / 96)
3 (**Complete Perfusion**.) - % (n/N)	47.4% (90 / 190)	55.3% (52 / 94)	39.6% (38 / 96)
2b-3*	75.8% (144 / 190)	81.9% (77 / 94)	69.8% (67 / 96)

*Two-sided group comparison Fisher's exact p-value = 0.063

mTICI After All Treatment	All Patients (n=198)	3D / Penumbra System (N=98)	Penumbra System (N=100)
0 (**No Perfusion**.) - % (n/N)	7.8% (15 / 192)	7.4% (7 / 95)	8.2% (8 / 97)

1 (**Penetration With Minimal Perfusion**.) - % (n/N)	1.0% (2 / 192)	1.1% (1 / 95)	1.0% (1 / 97)
2a (Partial filling.) - % (n/N)	8.9% (17 / 192)	4.2% (4 / 95)	13.4% (13 / 97)
2b (**Partial filling**) - % (n/N)	30.7% (59 / 192)	29.5% (28 / 95)	32.0% (31 / 97)
3 (**Complete Perfusion**.) - % (n/N)	51.6% (99 / 192)	57.9% (55 / 95)	45.4% (44 / 97)
2b-3*	82.3% (158 / 192)	87.4% (83 / 95)	77.3% (75 / 97)

*Two-sided group comparison Fisher's exact p-value = 0.089

eTable 6. Number of Patients Randomized by Center

#	Site Number	Randomized Patients	Randomized: Separator 3D with Penumbra System	Randomized: Penumbra System Alone
1	00518	35	18	17
2	00205	23	11	12
3	00431	18	9	9
4	00084	11	5	6
5	00017	10	5	5
6	00033	10	5	5
7	00110	10	5	5
8	00673	10	6	4
9	00041	9	5	4
10	00213	8	4	4
11	00203	8	4	4
12	00028	7	4	3
13	00245	7	3	4
14	00358	7	4	3
15	00035	4	2	2
16	00200	4	1	3
17	00253	3	1	2
18	00283	3	2	1
19	00023	2	1	1
20	00220	2	1	1
21	00387	2	1	1
22	00116	2	1	1
23	00412	1	0	1
24	00625	1	0	1
25	00113	1	0	1
-	**TOTAL**	**198**	**98**	**100**

eTable 7. Comparison of Baseline Characteristics of Analyzed and Missing Data by Group (Intention to Treat)

	Included in d90 mRS Analysis (N=182)	Missing from d90 mRS Analysis (N=16)	p-value
3D / Penumbra System, %	47.3% (86/182)	75.0% (12/ 16)	0.0388
Age, mean (SD)	67.1 (12.89)	64.4 (14.45)	0.4678
Female, %	56.0% (102/182)	56.3% (9/ 16)	1.0000
Baseline NIHSS, median [IQR]	18.0 [14.0, 21.0]	21.0 [13.5, 23.5]	0.5458
Admission systolic BP, mean (SD)	142.2 (20.43)	145.3 (20.80)	0.6102
Hypertension, %	78.0% (142/182)	81.3% (13/ 16)	1.0000
Diabetes, %	27.5% (50/182)	18.8% (3/ 16)	0.5660
Atrial fibrillation, %	49.5% (90/182)	37.5% (6/ 16)	0.4387
Site of primary occlusion, %:			
ICA	20.3% (37/182)	12.5% (2/ 16)	0.5332 [1]
MCA M1	62.1% (113/182)	81.3% (13/ 16)	
MCA M2	14.3% (26/182)	6.3% (1/ 16)	
PCA	1.1% (2/182)	0.0% (0/ 16)	
Basilar	1.1% (2/182)	0.0% (0/ 16)	
Left hemisphere occlusion, %	50.0% (91/182)	43.8% (7/ 16)	0.7951
Stenosis proximal to the primary occlusion, %	8.8% (16/182)	25.0% (4/ 16)	0.0643
Pre treatment mTICI 0 or 1, %	93.4% (170/182)	93.8% (15/ 16)	1.0000
Treatment with IV tPA, %	65.4% (119/182)	87.5% (14/ 16)	0.0955
Time from symptom onset to IV rtPA (hr), median [IQR]	1.7 [1.4, 2.5]	1.5 [1.4, 2.0]	0.1832
Time from onset to hospital admission, minutes, median [IQR]	113.0 [47.0, 228.0]	91.0 [33.5, 193.5]	0.5375

[1] P-value based on ICA vs MCA (M1, M2) only

p-values based on Fisher exact test for categorical data and Wilcoxon rank sum test for continuous data.

eTable 8. mRS Sensitivity Analyses (Intention to Treat)
Sensitivity analyses for day 90 mRS 0 to 2 were conducted with patients administered IV alteplase > 3 hours from stroke symptom onset or having an mTICI score of 2a or greater prior to intervention excluded. Patients who received any additional therapies or adjunctive devices following the use of the Penumbra System (+3D) were imputed as an outcome failure.

	All Patients (N=198)	**3D / Penumbra System (N=98)**	**Penumbra System (N=100)**	**Difference (95% CI)**
90 day mRS 0-2, Rescue therapy imputed as failure,**%**	40.1% (73 / 182)	41.9% (36 / 86)	38.5% (37 / 96)	3.32% (-10.95%, 17.58%)
90 day mRS 0-2, Excluding subjects administered IV alteplase > 3 hours from symptom onset, **%**	44.2% (72 / 163)	44.3% (35 / 79)	44.0% (37 / 84)	0.26% (-15.00%, 15.51%)
90 day mRS 0-2, Rescue therapy imputed as failure, excluding subjects administered IV alteplase >3 hours from symptom onset,and excluding subjects with adjudicated baseline mTICI 2a-3, **%**	37.5% (57/152)	38.0% (27/71)	37.0% (30/81)	0.99% (-14.44%, 16.42%)

eTable 9. Screening Results

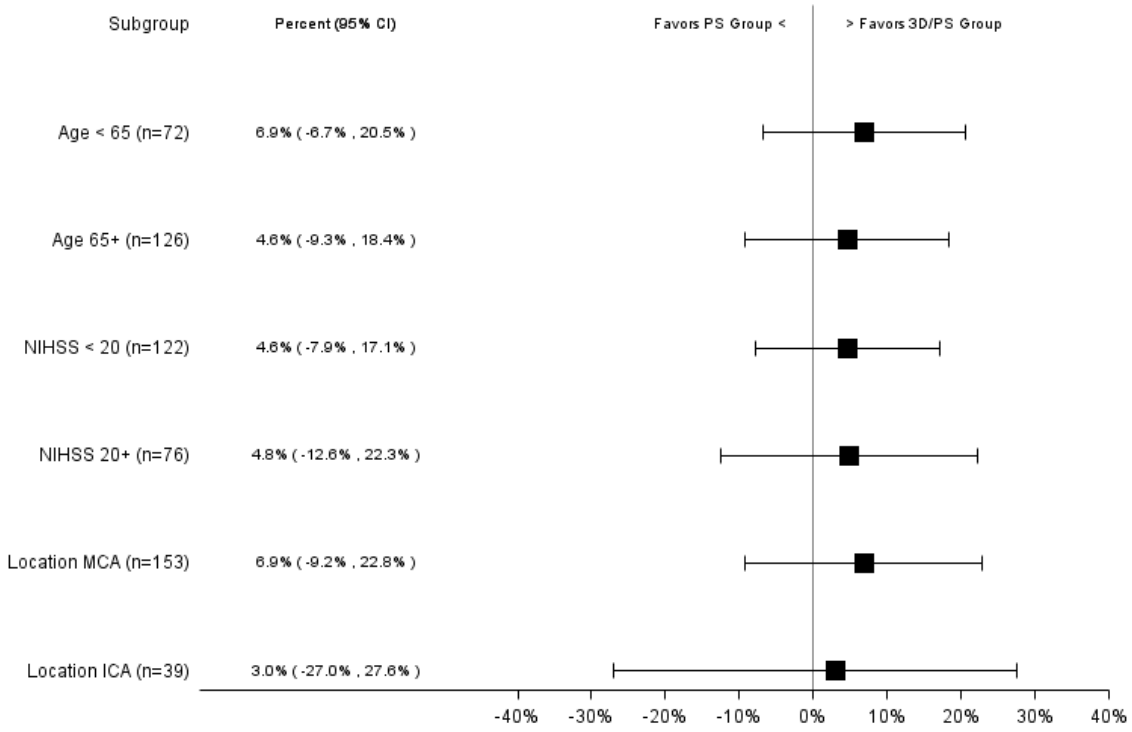
Patients were screened and not enrolled in the study based on the screening logs provided by 54 clinical study sites, of which 25 sites randomized patients into the trial. The categories reported for more than 5% of screen failures are provided in the table below.

Reason for Screen Failure	Number of patients
NIH Stroke Scale (NIHSS) score < 8	2878
Pre-existing neurological condition or psychiatric disease such as a pre-stroke mRS score of ≥ 1	1073
< 18 or > 85 years old	947
Presenting symptoms not consistent with an acute ischemic stroke for revascularization or > 8 hours from symptom onset	744
CT evidence of mass effect with midline shift, >1/3 of MCA territory infarcted, or ICH	477

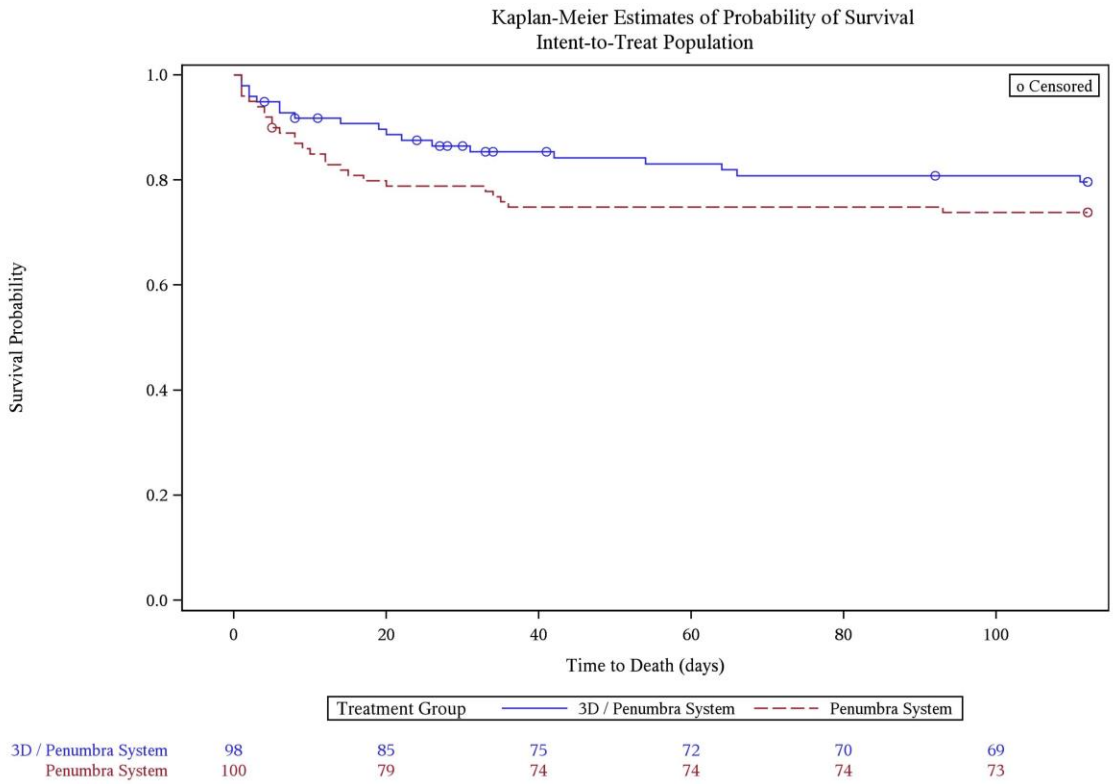
eTable 10. Classification of Intracebral Hemorrhages

Intracranial Hemorrhage [Patient % (n/N)]	All Patients (N = 198)	Penumbra System (N = 100)	3D / Penumbra System (N = 98)
Symptomatic Intracranial Hemorrhage within 24 hours ± 12 hrs	4.0% (8 / 198)	5.0% (5 / 100)	3.1% (3 / 98)
ECASS within 24 hours ± 12 hrs			
HI-1	2.5% (5 / 198)	4.0% (4 / 100)	1.0% (1 / 98)
HI-2	8.1% (16 / 198)	10.0% (10 / 100)	6.1% (6 / 98)
PH-1	9.1% (18 / 198)	11.0% (11 / 100)	7.1% (7 / 98)
PH-2	3.5% (7 / 198)	1.0% (1 / 100)	6.1% (6 / 98)
SAH within 24 hours ± 12 hrs	4.5% (9 / 198)	7.0% (7 / 100)	2.0% (2 / 98)
OTHER ICH within 24 hours ± 12 hrs	1.0% (2 / 198)	2.0% (2 / 100)	0.0% (0 / 98)

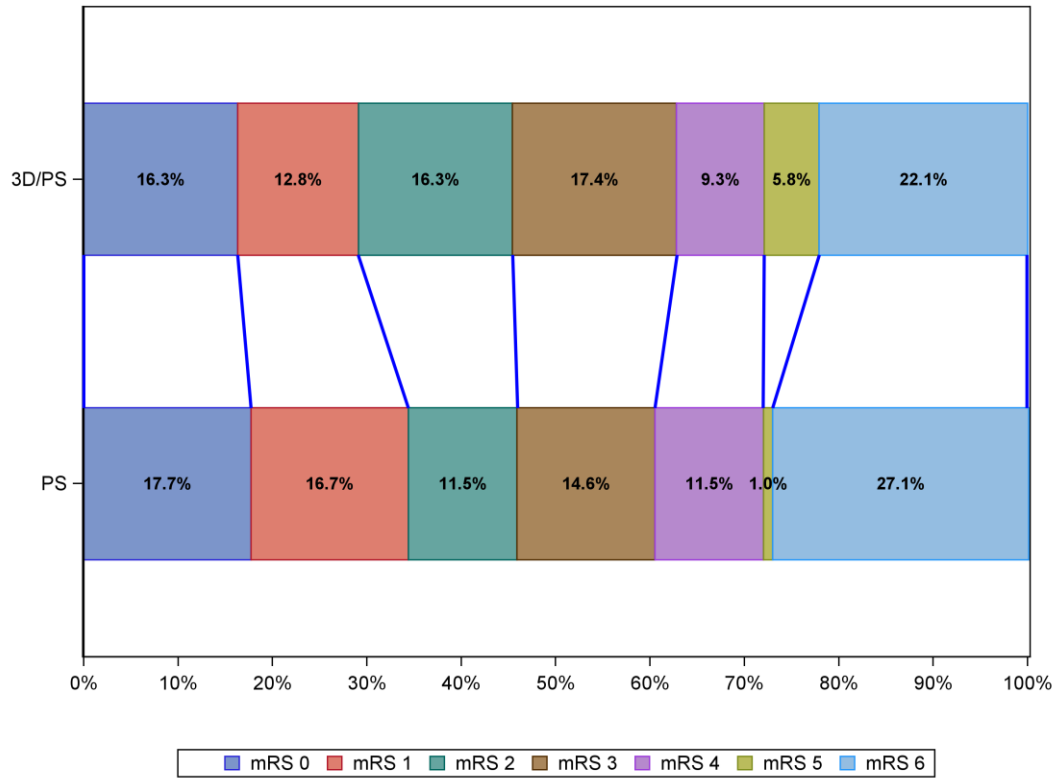
eFigure 1. Distribution of Primary End Point (mTICI 2-3) Treatment Effect Across the Prespecified Subgroups (Intention to Treat)



eFigure 2. Kaplan-Meier Estimates of the Probability of Death in Patients (Intention to Treat)



eFigure 3. Functional Outcomes at 90 Days, According to Modified Rankin Scale Score (Intention to Treat)



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