Evaluating Image-Guided, Minimally Invasive Surgery for ICH: MISTIE III Results

Daniel F. Hanley, MD
Mario Zuccarello, MD
Issam A. Awad, MD

Principal Investigators

On behalf of the MISTIE investigators, patients and families

NIH National Institute of Neurological Disorders and Stroke
JOHNS HOPKINS MEDICINE
THE UNIVERSITY OF CHICAGO MEDICINE
UNIVERSITY OF Cincinnati
NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

Disclosures

Daniel F. Hanley, MD (Physician Co-chair)

- MISTIE III support: NIH/NINDS grant U01NS080824; Genentech donation of alteplase for North American sites
- Unlabeled/unapproved use: IND #8523 (intracerebral use of rt-PA)
- Consulting: BrainScope, Neurotrope, Op2Lysis, Portola Pharmaceuticals, Medtronic (legal opinions)

Issam A. Awad, MD, MSc, FACS (Surgeon Co-chair)

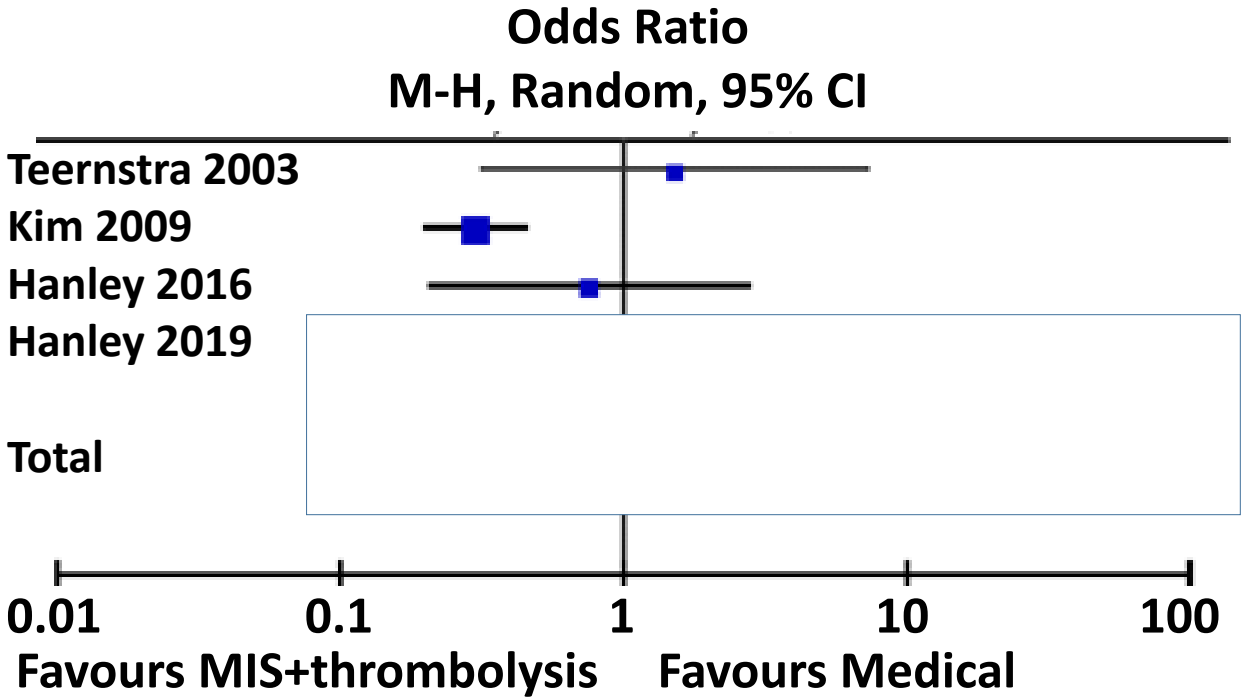
- NIH/NINDS support (U01NS080824) as MISTIE III trial co-chair and surgical center director

For disclosures for all MISTIE III authors, see the trial results paper in *The Lancet* (published online 2-7-2019).

Do MISTIE II results generalize?

"There is no evidence to support surgical intervention on a routine basis to improve outcome after supratentorial ICH in comparison with conservative management." — ESO guidelines

Prior MISTIE Trials



MISTIE III Goals

1) Define functional and/or mortality change
2) Safety of surgery-drug combination
3) Impact of procedural performance on outcome

MISTIE III Trial Goals

Safety goal:

Our trial evaluated the MISTIE procedure. We hoped to achieve clot evacuation without procedure-related safety events beyond the risks associated with standard care in an intensive care unit.

Primary hypothesis:

Does ICH reduction via the MISTIE procedure alter functional outcomes in patients with large ICH?

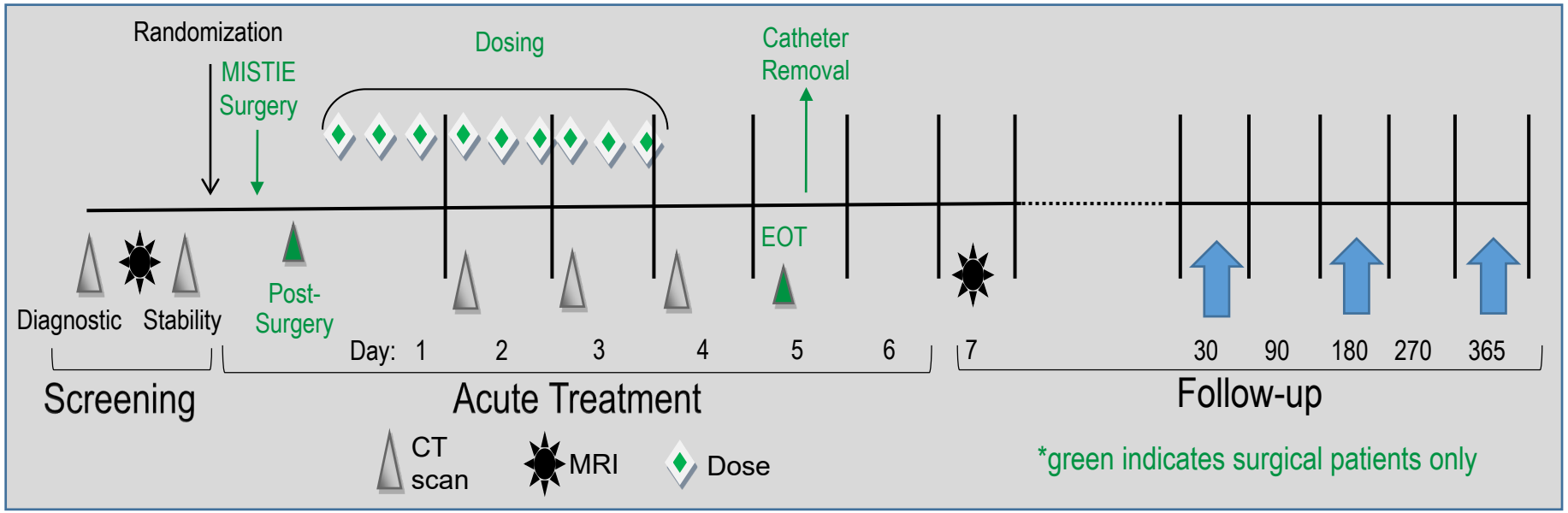
Clinical Protocol

Inclusion Criteria

- ICH ≥30 mL
- ICH/IVH/IVH catheter tract/BP stability
- Randomize 12 to 72 hours post onset
- Age ≥18 years
- Historical modified Rankin Scale score ≤1

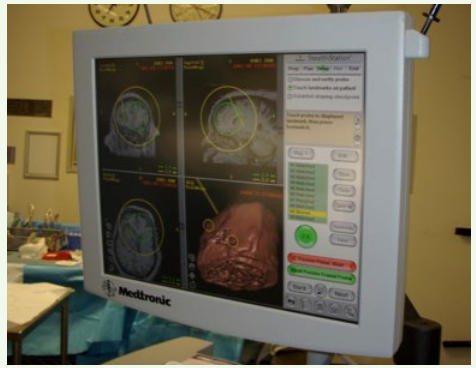
Exclusion Criteria

- Vascular defect R/O by CTA
- Infratentorial hemorrhage; evidence of brain stem involvement; large IVH
- Anticoagulation required; irreversible platelet count <100,000 or INR >1.4
- Uncontrollable systemic bleeding
- Other comorbidity preventing use of thrombolytic therapy or follow-up

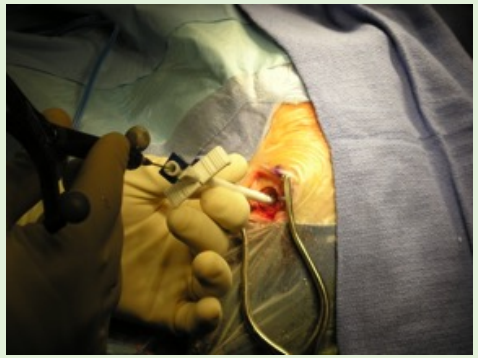


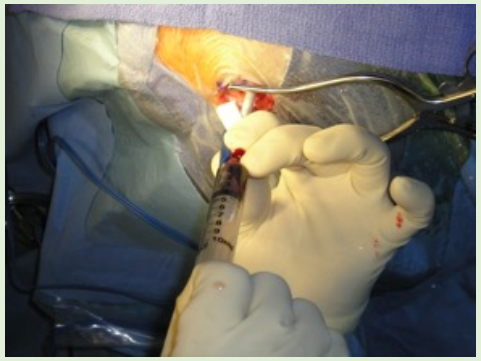
MISTIE Surgical Task

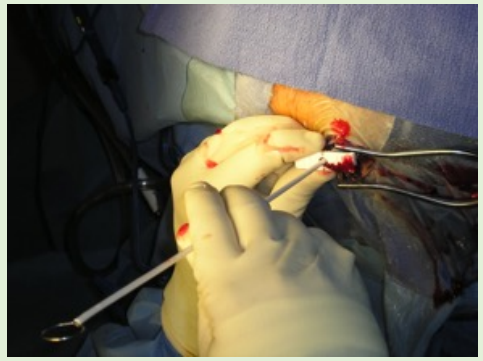
Navigation



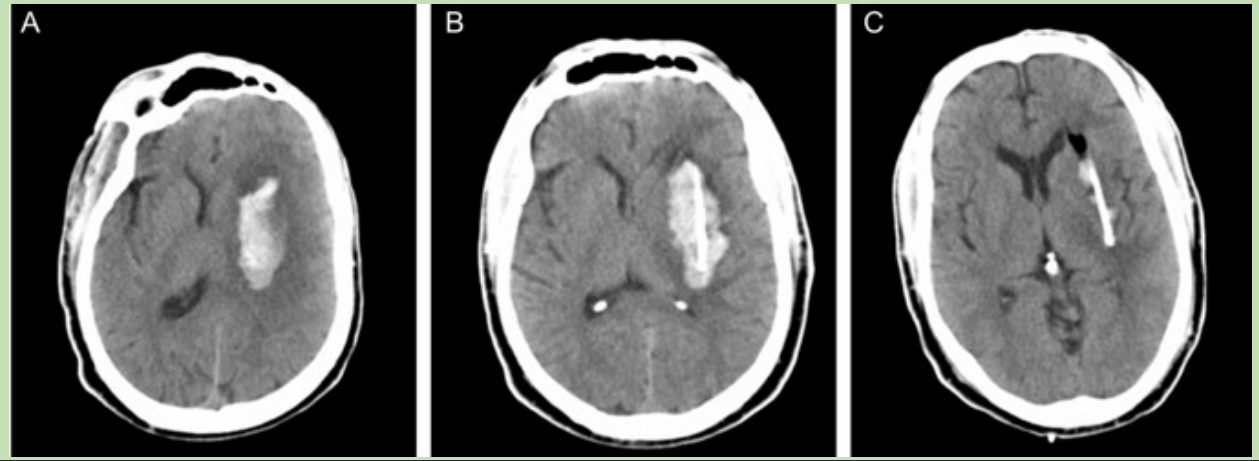
Catheter Steps







Treatment Imaging



MISTIE III: An Investigator-Initiated Trial

Novel trial execution

- Adaptive randomization
- Standard surgical task
- Core surgical laboratory
- Blinded adjudication mRS

ClinicalTrials.gov:
NCT01827046

Primary outcome

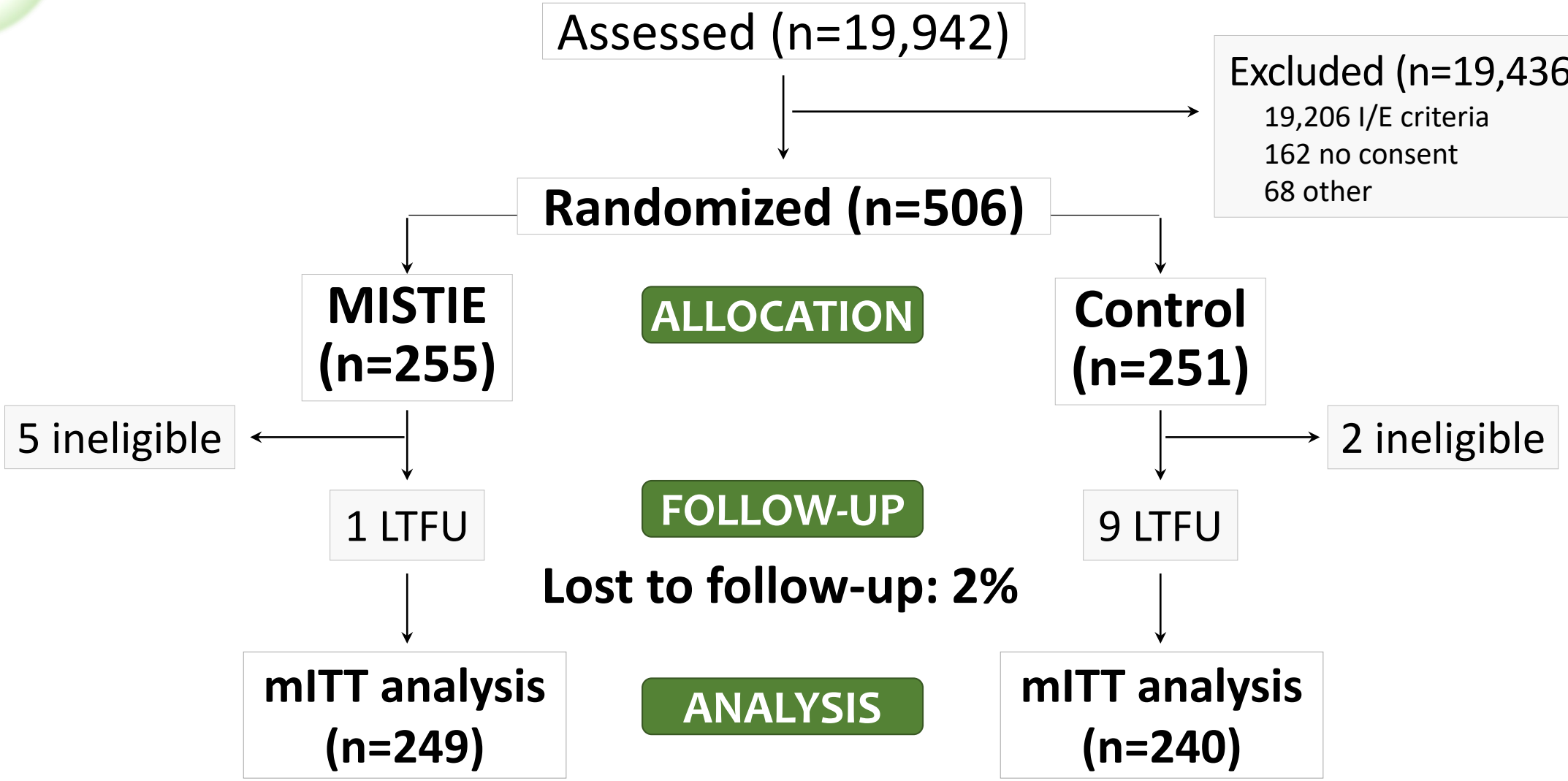
- % mRS 0–3 at 365 days
- Sensitivity analyses: ordinal; site

Secondary outcomes

- eGOS USD–UGR (4–8) at 365 days
- All-cause mortality at 365 days
- Surgical success in relation to 365-day mRS

Safety: Safety at 30 days

MISTIE III CONSORT Diagram



Demographics and Comorbidities

	MISTIE (n=250)	Control (n=249)
Age (years)	62 (52–70)	62 (53–71)
Sex: Male	159 (64)	146 (59)
Race		
Black	46 (18)	41 (16)
White	190 (76)	184 (74)
Other	14 (5)	24 (9)
Hispanic/Latino	34 (13)	34 (14)
Tobacco use	50 (20)	39 (16)
Cocaine use	11 (4)	9 (3)
Anticoagulated	24 (9)	10 (4)
HRT	1 (0.4)	3 (1)
Hyperlipidemia	96 (38)	93 (37)
Antiplatelet	67 (27)	77 (31)
Diabetes	72 (29)	67 (27)
Hypertension	241 (96)	240 (96)
Other CVD	38 (15)	34 (14)

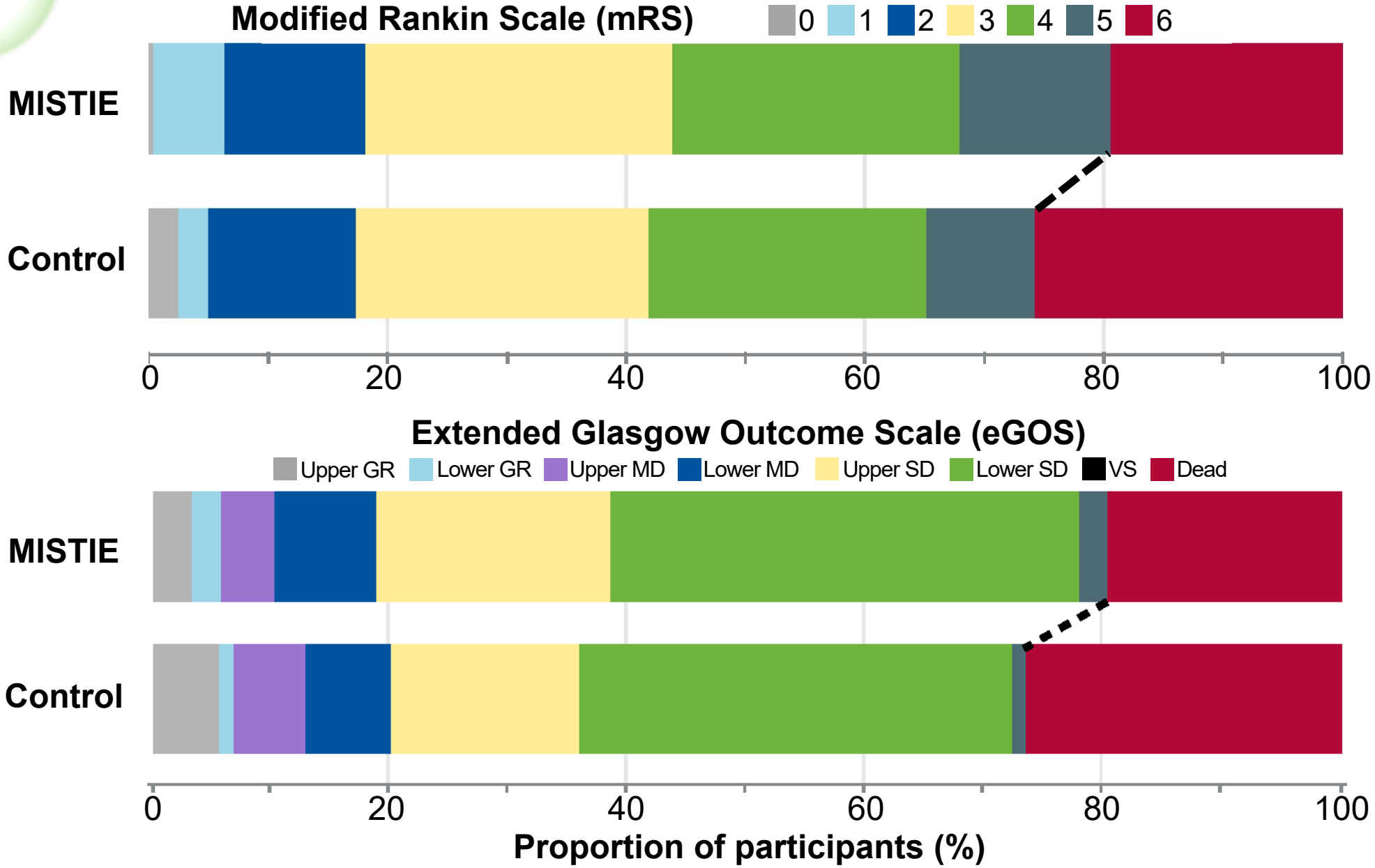
Baseline Characteristics

		MISTIE (n=250)	Control (n=249)
GCS score	3–8 9–12 13–15	64 (26) 111 (44) 75 (30)	63 (25) 108 (43) 78 (31)
NIHSS score		19 (15–23)	19 (15–23)
Diagnostic CT (mL)	ICH volume IVH volume	43 (30–54) 0 (0–2)	41 (31–55) 0 (0–2)
Stability CT (mL)	ICH volume IVH volume	46 (35–60) 0.3 (0–3.1)	45 (35–57) 0.4 (0–3.2)
Hours from ictus	Diagnostic CT Stability CT	2 (1–6) 36 (23–53)	2 (1–5) 36 (24–49)
BP at presentation (mm Hg)	Systolic Diastolic	177 (155–208) 99 (85–113)	176 (158–200) 98 (84–114)
Clot location	Deep	163 (65)	144 (58)
Historic mRS score	0 1	230 (92) 20 (8)	233 (94) 16 (6)

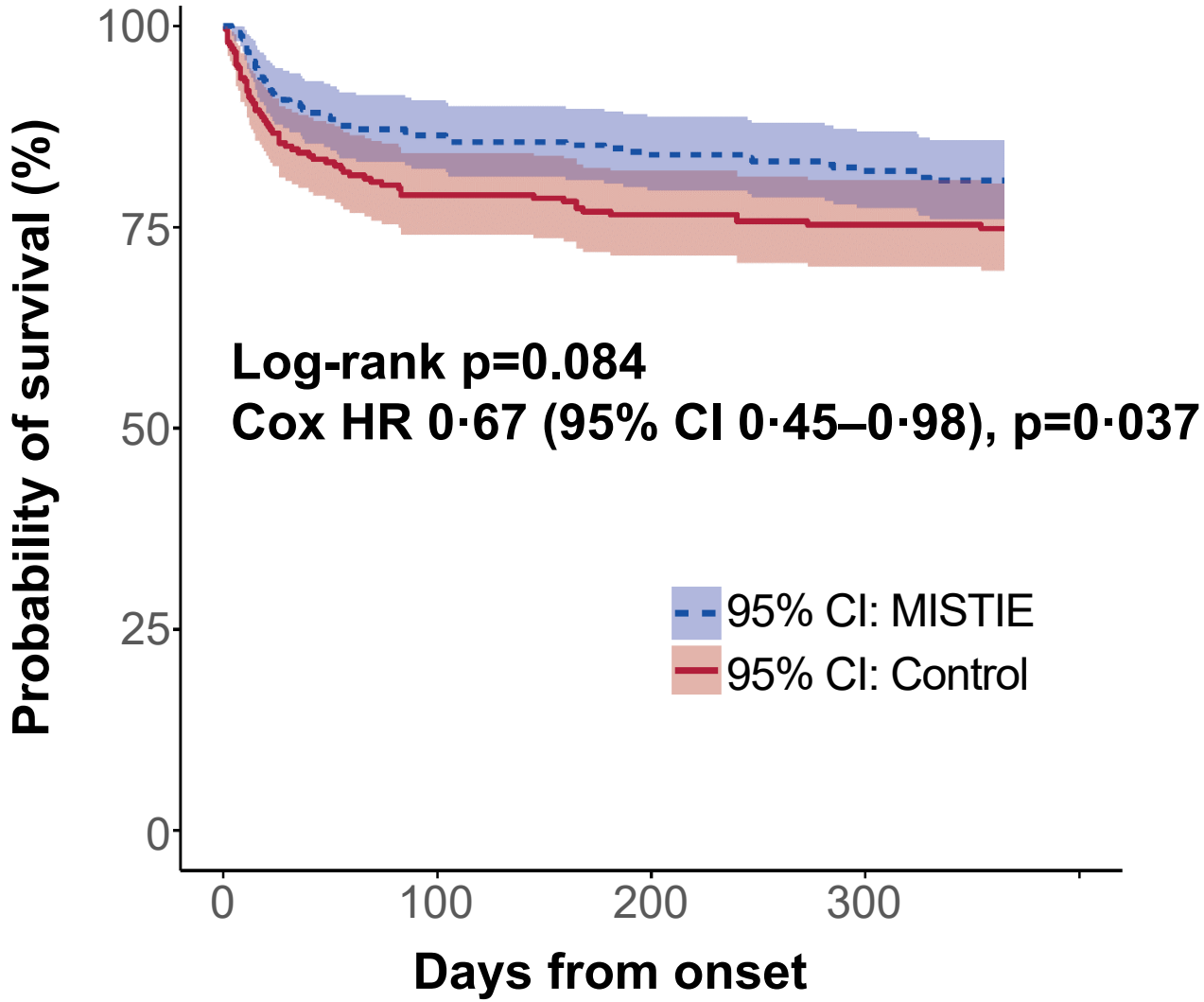
Treatment Variables

	MISTIE (n=250)	Control (n=249)	p value
Ictus to randomization (h)	47 (33-60)	46 (36-58)	0.817
Ventilation at randomization	107 (43)	102 (41)	0.678
MISTIE procedure duration (h)	1 (1-1)	NA	NA
Number of doses	4 (2-6)	NA	NA
Ictus to end of treatment (EOT) (h)	127 (107-151)	123 (113-134)	<0.001
EOT CT			
ICH volume (mL)	12 (8-21)†	44 (34-56)†	<0.001
IVH volume (mL)	0.2 (0-1.5)	0.3 (0-1.9)	0.137
EOT ICH remaining ≤15 mL	148 (60)	2 (0.8)	<0.001
ICP monitored	34/250 (14%)	38/249 (15%)	0.598
% subjects with any ICP ≥20 mm Hg	9/34 (26%)	22/38 (58%)	0.007
% subjects with any CPP <70 mm Hg	21/34 (62%)	31/38 (82%)	0.06
% ICP readings ≥20 mm Hg	23/690 (3%)	67/711 (9%)	0.01
% CPP readings <70 mm Hg	64/690 (9%)	159/711 (22%)	0.04
One or more ICP therapies	25/34 (73%)	26/38 (68%)	0.634
Days in ICU	10 (7-17)	10 (5-16)	0.460
Withdrawal of care	26 (10)	35 (14)	0.213
Days to return home	55 (34-105)	62 (35-100)	0.846

Primary Result: Function at 365 Days

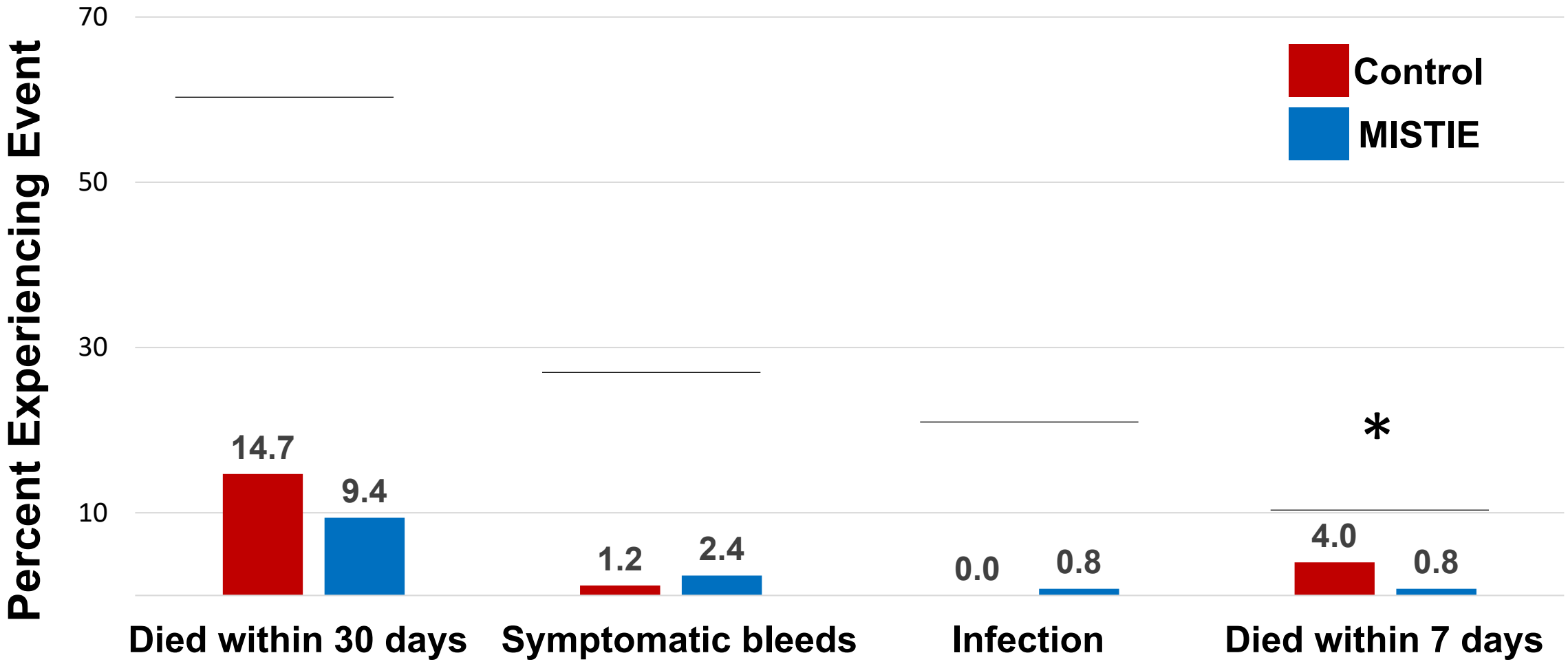


Kaplan-Meier Survival Estimates: 365 Days

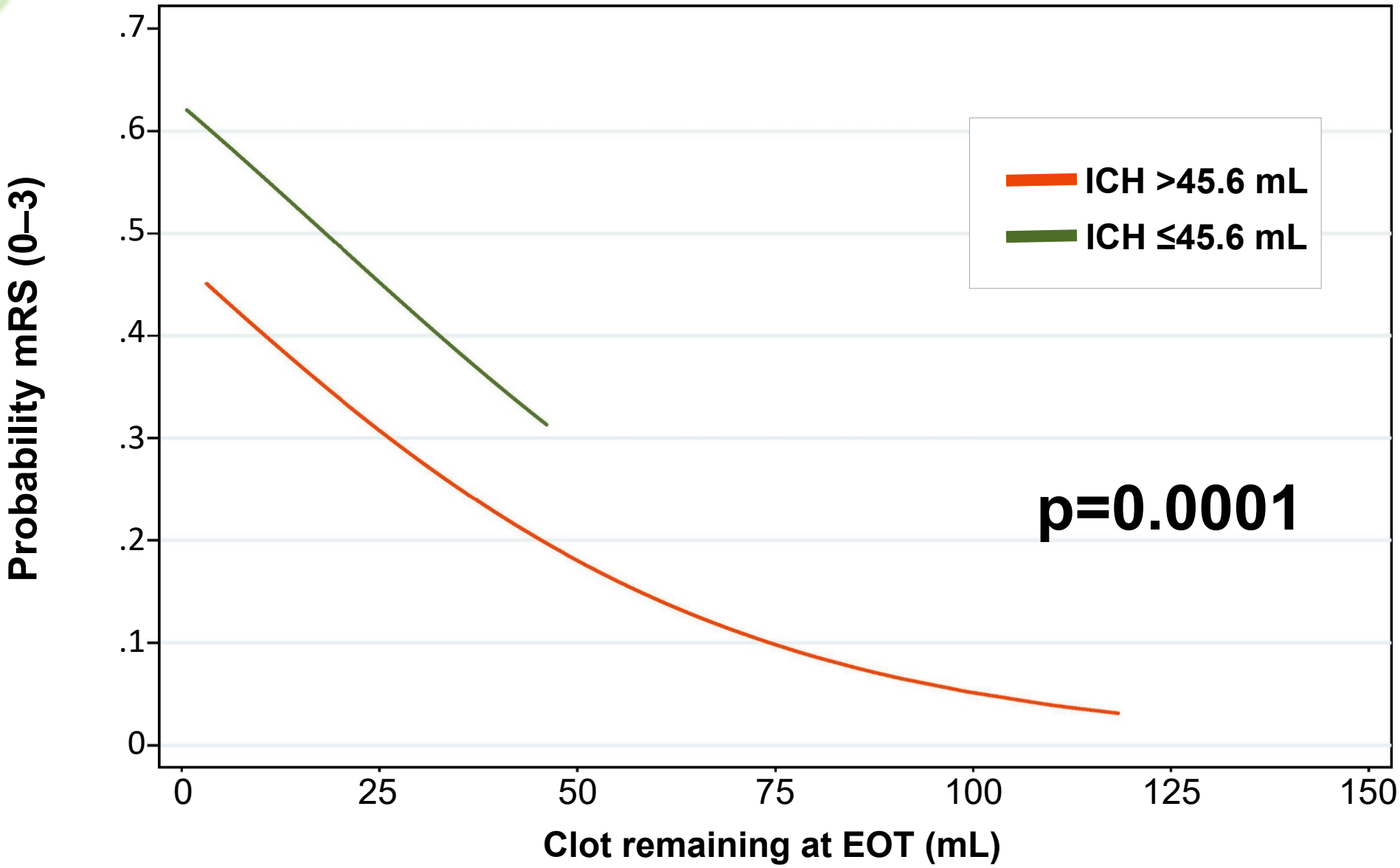


Number at risk: 499 409 397 385

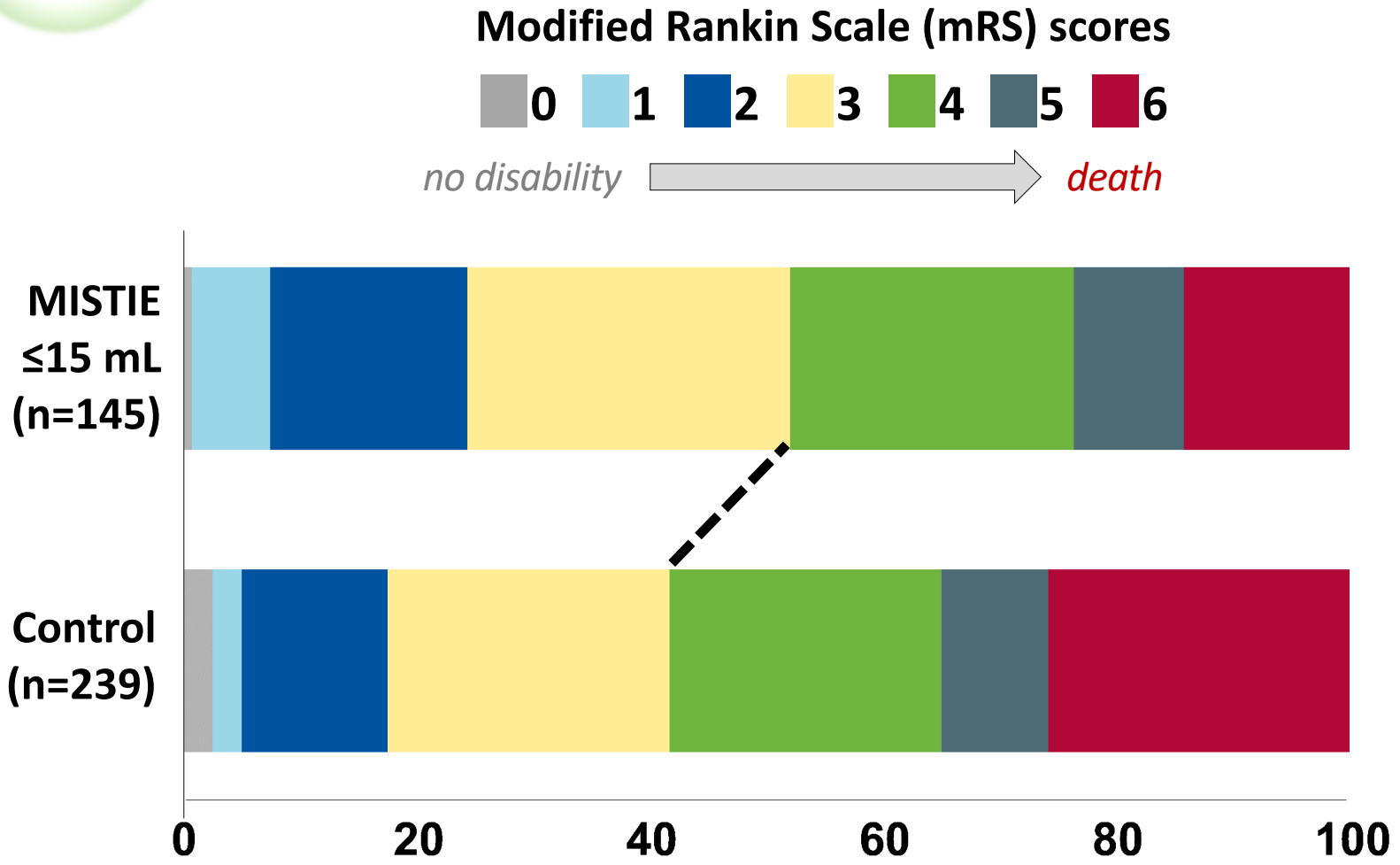
Safety Events



Good Functional Outcome vs Clot Remaining at EOT



mRS Distributions at Day 365 (As Treated)



mRS	MISTIE ≤15 mL (n=145)	Control (n=239)
0	1 (0.7%)	6 (2.5%)
1	10 (6.9%)	6 (2.5%)
2	25 (17.2%)	30 (12.6%)
3	41 (28.3%)	58 (24.3%)
4	35 (24.1%)	56 (23.4%)
5	14 (9.7%)	22 (9.2%)
6	19 (13.1%)	61 (25.5%)

10.5% difference mRS 0-3 (95% CI 1.0–20.0; p=0.03)

Overview of Results

Primary & Sensitivity Analysis				
1.1	Functional outcome	mRS 0-3 not different	Risk diff=4%	p=0.33
1.2a-f	Ordinal mRS	mRS=6 less likely: MISTIE	AOR=0.6	p=0.03
1.2d-e	Subgroup analyses	No difference by treatment arm	No difference	NS

Ordered Secondary Analyses				
2.2	All-cause mortality	Lower hazard of death: MISTIE	HR=0.67	p=0.037
2.3	Clot removal	Clot removal=better function	AOR=0.68	p<0.001
2.3a	EOT ≤15 mL (surgical target)	Increased % mRS 0-3	Risk diff=10.5%	p=0.03
2.6	ICU duration	No difference	10 vs 10	p=0.46
2.8-2.9	30-day mortality	Less mortality in MISTIE	9.4% vs 14.3%	p=0.09
	Safety: AEs/SAEs	More total SAE: Control	126 vs 142	p=0.01

Conclusions

Goal 1: *Define functional and/or mortality change*

- For ITT, where 40% of the cases did not meet the treatment goal, MISTIE did not reach the postulated goal
- Frequency of survival is modestly improved with MISTIE without a “price” in surgical risk or vegetative state

Goal 2: *Safety of surgery-drug combination*

- MISTIE can be safely performed with simple training

Goal 3: *Impact of procedural performance on outcome*

- Improved function and increased survival is produced with Surgical reduction to ≤15 mL

Thanks

To the Patients, Families and Investigative Teams at 78 sites and our Consortium Partners all of whom made MISTIE III possible.

MISTIE III

Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial

Daniel F Hanley, Richard E Thompson*, Michael Rosenblum, Gayane Yenokyan*, Karen Lane*, Nichol McBee*, Steven W Mayo*, Amanda J Bistran-Hall, Dheeraj Gandhi, W Andrew Mould, Natalie Ullman, Hasan Ali, J Ricardo Carhuapoma, Carlos S Kase, Kennedy R Lees*, Jesse Dawson, Alastair Wilson, Joshua F Betz, Elizabeth A Sugar*, Yi Hao, Radhika Avadhani, Jean-Louis Caron, Mark R Harrigan, Andrew P Carlson, Diederik Bulters, David LeDoux, Judy Huang, Cully Cobb, Gaurav Gupta, Ryan Kitagawa, Michael R Chicoine, Hiren Patel, Robert Dodd, Paul J Camarata, Stacey Wolfe, Agnieszka Stadnik, P Lynn Money, Patrick Mitchell, Rosario Sarabia, Sagi Harnof, Pal Barzo, Andreas Unterberg, Jeanne S Teitelbaum, Weimin Wang, Craig S Anderson, A David Mendelow*, Barbara Gregson*, Scott Janis*, Paul Vespa*, Wendy Ziai*, Mario Zuccarello*, Issam A Awad*, for the MISTIE III Investigators†*

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MISTIE ISC Presentations

Date	Time	Session	Session/Abstract ID	Location	Presenter	Title
2/6	7:00 - 7:12am	Intracerebral Hemorrhage Oral Abstracts I	Intracerebral Hemorrhage	Kalākaua Ballroom C	Andrew Mould	Reduction in Perihematomal Edema Leads to Improved Clinical Outcomes: Results from the MISTIE III Trial
2/6	9:23 - 9:42am	Big Picture on Intracerebral Hemorrhage: Practical Implications and Future Outlook	Intracerebral Hemorrhage	Room 316BC	Wendy Ziai	Intracranial Pressure and Cerebral Perfusion: Impact in ICH?
2/6	6:30 - 7:00pm	One-on-One Time for an Individual Q&A with Poster Presenters	LBP8	Poster Hall, Hall 1	Lauren Sansing	Dynamic Profiling of Leukocytes From the Blood and Brain of Intracerebral Hemorrhage (ICH) Patients: Results From ICHseq
2/7	11 - 11:12am	Invited Symposium	Invited Symposium	Hall 3	Dan Hanley	MISTIE 3 Trial Results
2/7	11:12 - 11:24am	Invited Symposium	Invited Symposium	Hall 3	Issam Awad	MISTIE III Surgical Results: Efficiency of Hemorrhage Removal Determines mRS