Benefits o... ...troke Unit
C... ...nt:

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Prospective, Multicenter, Controlled Trial of Mobile Stroke Units

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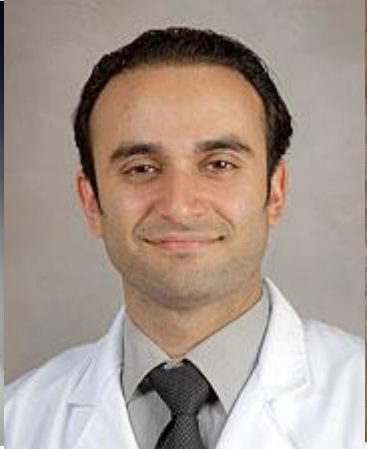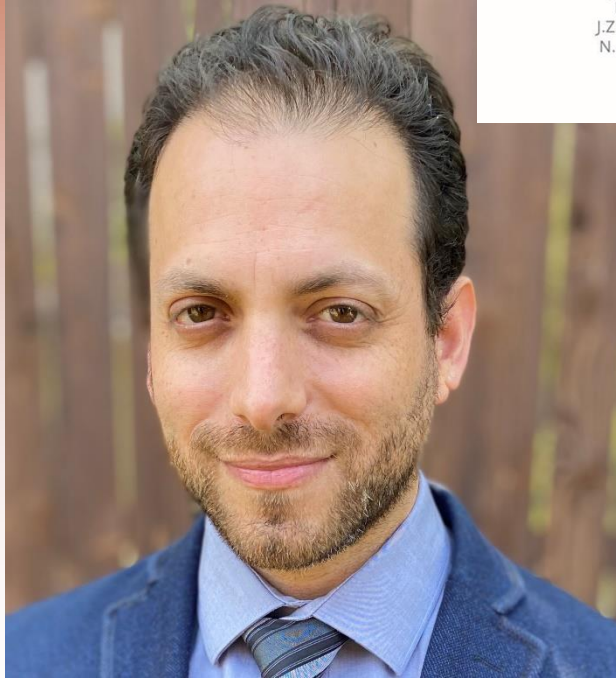
Alex Czap MD,   Ritvij Bowry MD

Disclosures

- Funding: PCORI, AHA
- Genentech donated Activase
- Consultant for Frazer Ltd (Grotta, Parker)

Houston 2014
Ritvij Bowry, Suja Rajan, Nicole Gonzales, Mengxi Wang, David Persse, Asha Jacob, Michael Gonzales, Noopur Singh

Colorado (Aurora and Colo Spgs) 2017
William Jones, Brandi Schimpf, Kim Ackerson

Memphis 2017
Anne and Andrei Alexandrov
Jim Rhudy

New York 2018
Matt Fink, Babak Navi
Carla Sherman, Josh Willey

LA-UCLA 2018
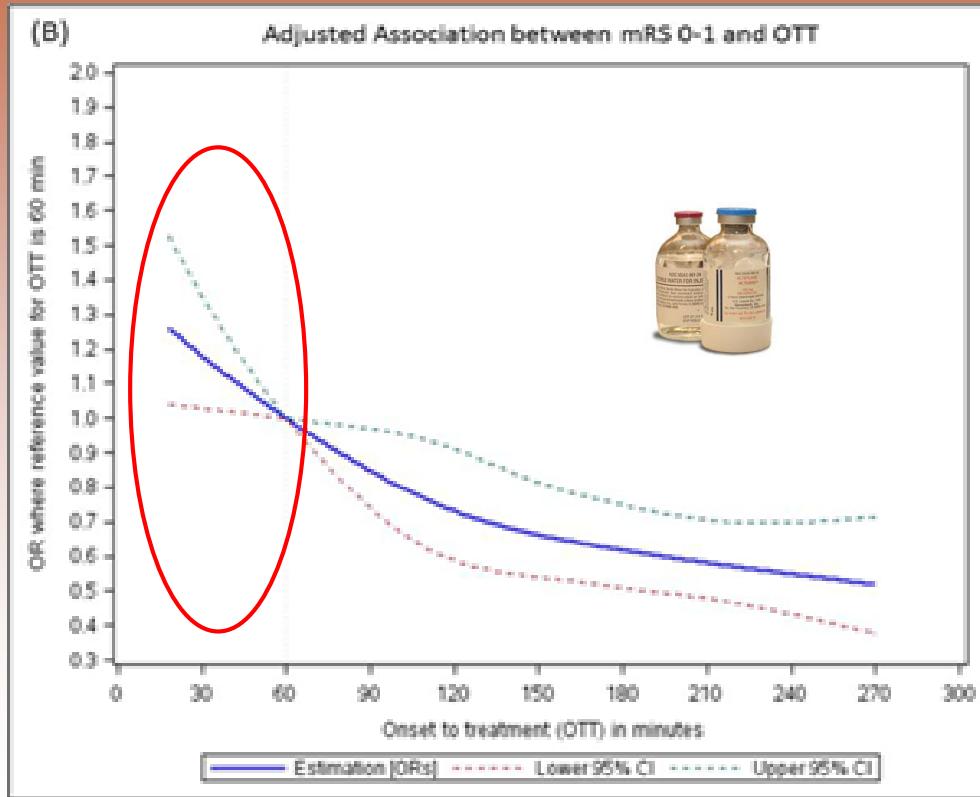May Nour, Jeff Saver
Kevin Brown, Bryan Villareal

Sutter-Peninsula 2019
Ilana Spokoyny, Joey English
Jenny Im, Nobl Barazangi

Indianapolis 2019
Jason Mackey, Sarah Collins, Kelly Silnes

The most potent way to improve tPA outcomes is to give it faster--
Especially in the first "golden hour" after onset

(B) Adjusted Association between mRS 0-1 and OTT

The only way to accomplish this….
Is to bring the treatment to the patient

Kim et al, GWTG, Circulation 11/4/16

Houston Mobile Stroke Unit— First in U.S. 2014

- ✓ Standard 12 foot ambulance
- ✓ Portable CT scanner
- ✓ Point-of-care laboratory
- ✓ Tele-radiology & neurology
- ✓ VN, RN, CT tech, Medic
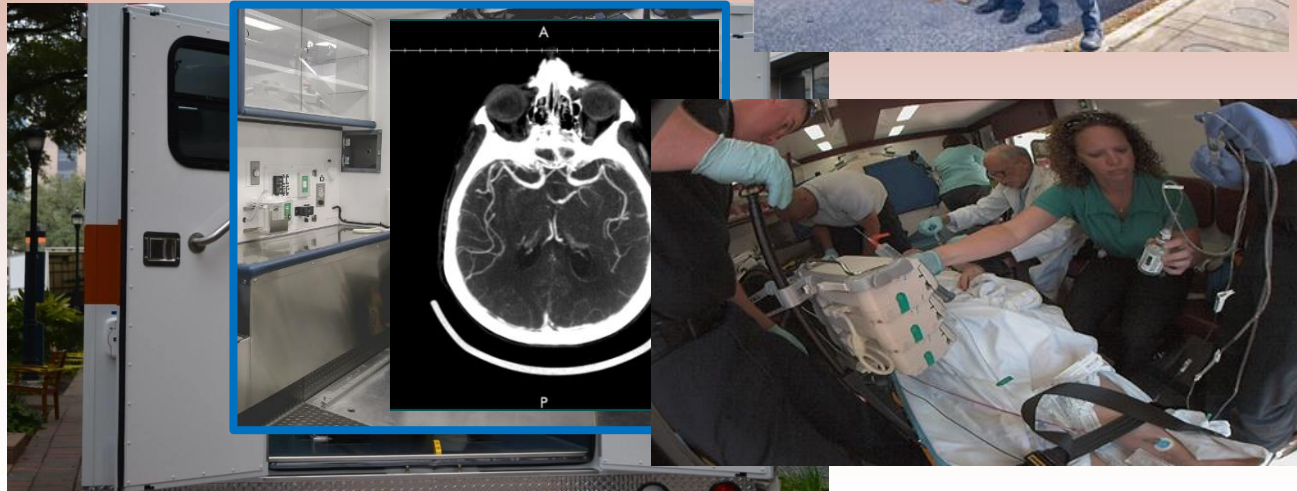
A Tour of the Houston Mobile Stroke Unit

The on board MD can be replaced by a TM MD

Satisfactory connectivity
169/173 (98%) of MSU consults

Agreement between On-Board and TM VN
88% (Kappa = 0.73)
(compared with in-person agreement in ED of 88%)

	Physician	N	Mean	SD
MSU Arrival to tPA Decision (minutes)	OB	163	18.9	7.7
	TM	39	21.2	7.6
MSU Arrival to tPA Bolus (minutes)	OB	110	24.1	6.3
	TM	26	23.6	6.4

Wu et al. Stroke 2017; 48:493-97, Ramadan et al. Stroke. 2017; 48:222-24

The MSU Facilitates the Entire Stroke Treatment Pathway

65 yo M
Onset 10:35 pm
Rendezvous 11:12 (37 min)
NIHSS 24

tPA (MSU)   11:22 (**47 min from onset**)
CTA (MSU)   11:27
Call to ET team

ED door 11:46
GP   11:56 (**DTGP 10 min**)
Recan   12:26 (111 min)

24 hr NIHSS 3
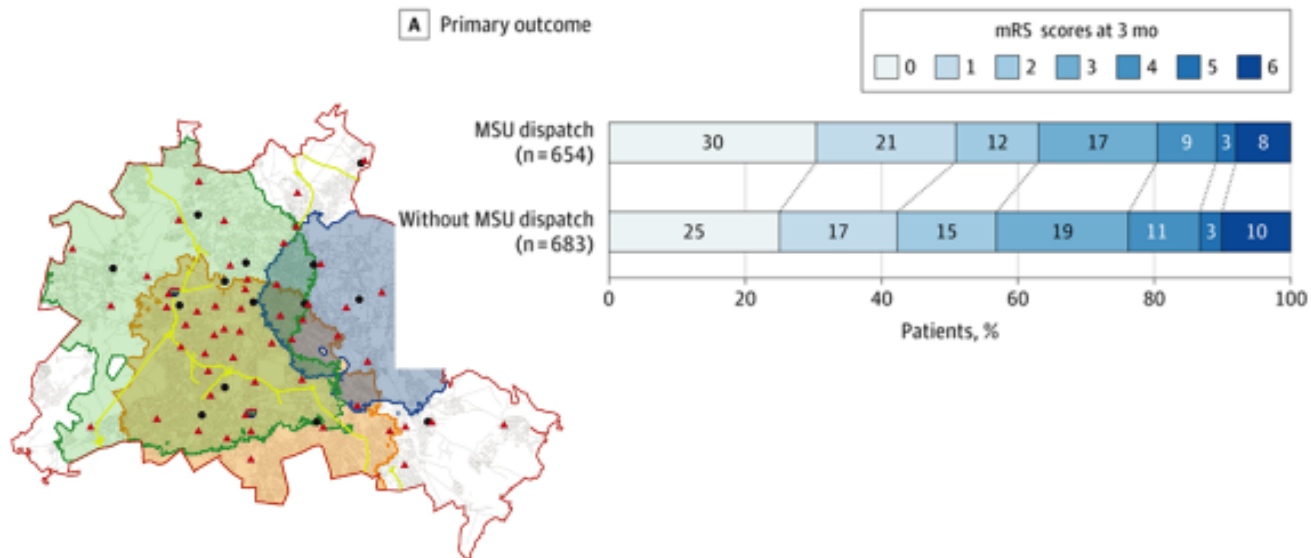
BEST-MSU Study

Hypothesis:
- Compared with Standard Management (SM) by EMS…….MSU management will….
  - SA-1: reduce disability measured 90 days after stroke,
  - SA-2: reduce health care resource utilization over the subsequent year

Design
- Phase III alternating week (MSU or SM) cluster-controlled

Inclusion Criteria
- Primary analysis population - all tPA eligible patients (mITT)

Outcome
- Primary - Utility-weighted mRS (uw-mRS) at 3 mo
    0.07 difference (initially was 0.09)
    Sample size 1038 (blindly increased based
       on results from Phantom-S study showing
       0.07 difference)
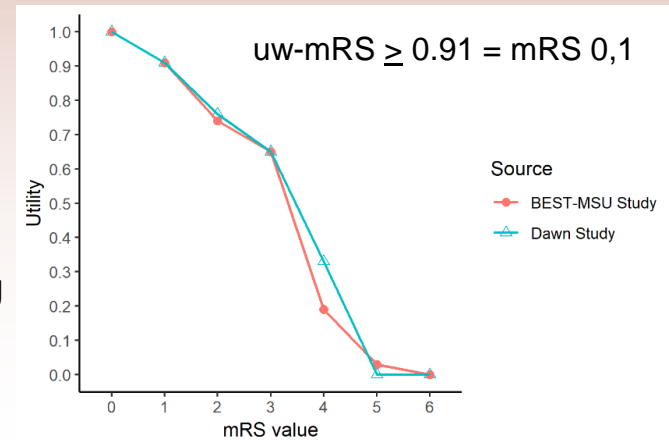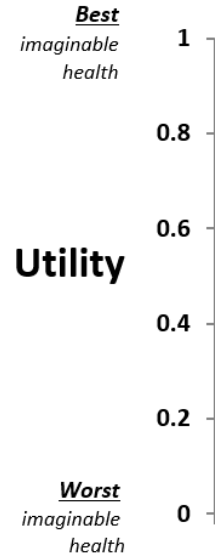
uw-mRS $\geq$ 0.91 = mRS 0,1

Quality of Life Utility vs. Modified Rankin Score

Best
*imaginable
health*

1 –

0.8 –

0.6 –

Utility

0.4 –

0.2 –

Worst
*imaginable
health*

0 –

Quality of Life Utility vs. Modified Rankin Score
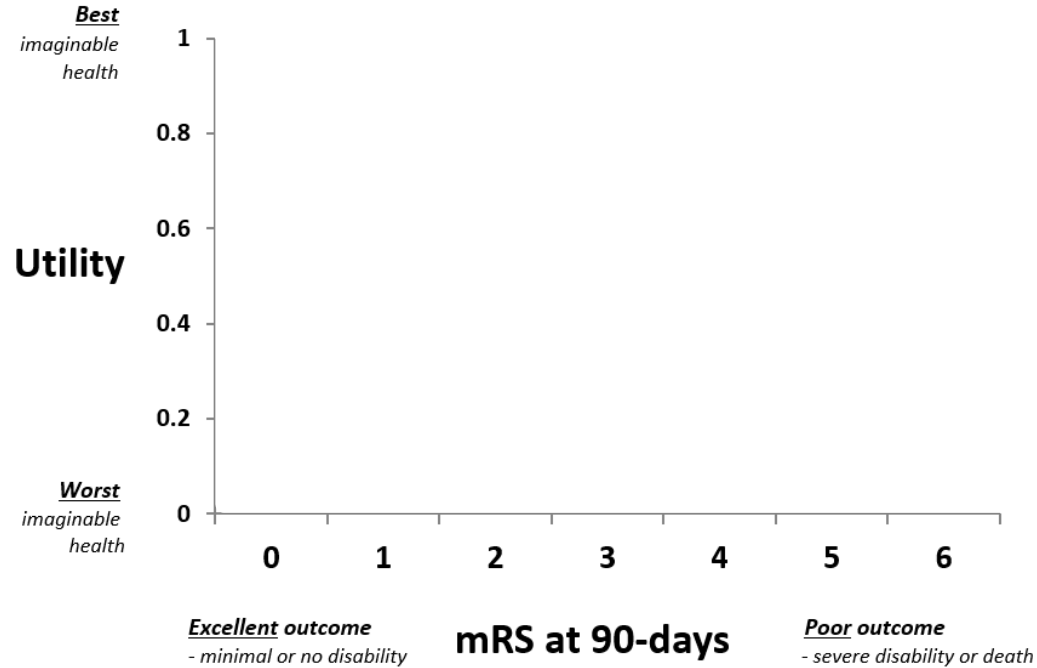
Quality of Life Utility vs. Modified Rankin Score
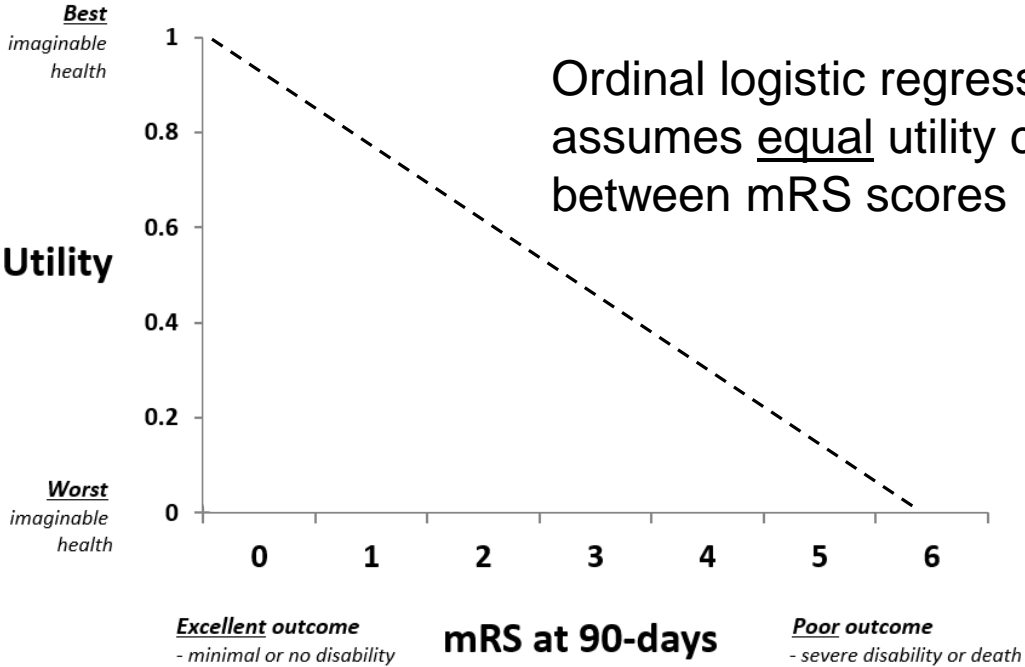
Quality of Life Utility vs. Modified Rankin Score
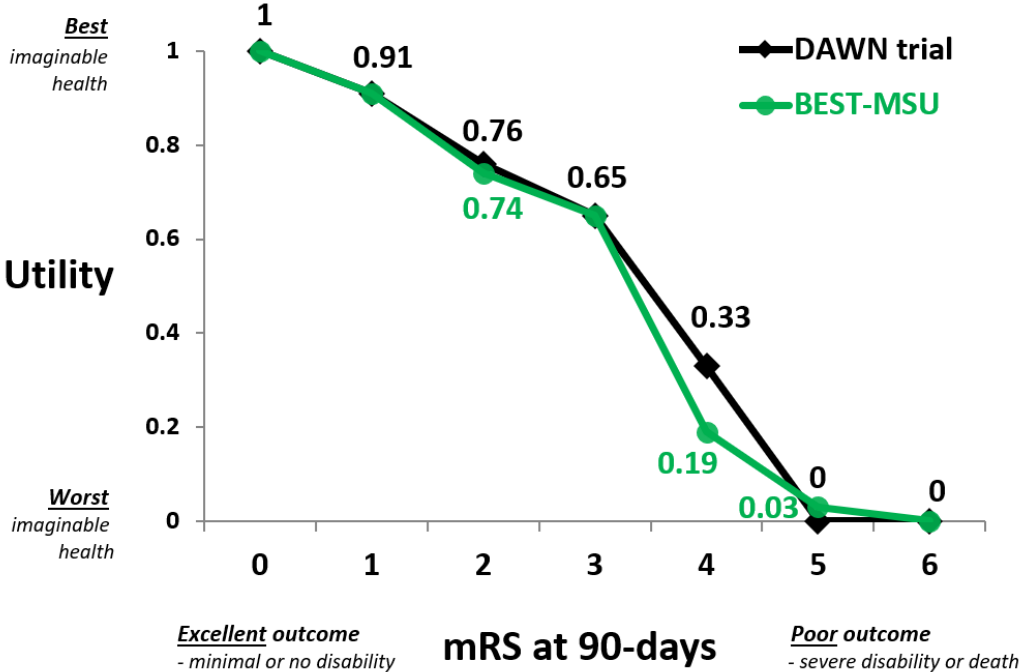
BEST-MSU Study Process- avoiding bias

1. MSU / SM alternating weeks
   <u>MSU weeks</u>

   911 call → EMS ambulance immediately dispatched per routine → MSU team dispatched to site → MSU team meets EMS ambulance at emergency site
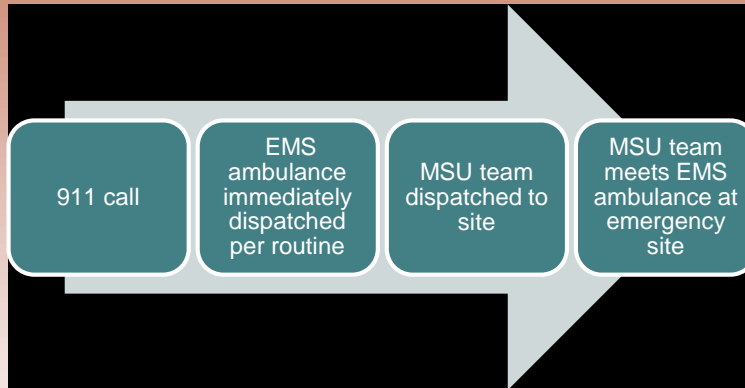
   <u>SM weeks</u>
   MSU team dispatched without MSU to ensure comparable pts.

2. Blinded Adjudication of tPA eligibility (primary analysis population)
3. Blinded assessment of 90d mRS using standardized tool (RFA)

Rendezvous:
allows one MSU to cover 75% of an entire city of 2.5 M
Parker et al 2019

- Direct 911 dispatch-- median **7 miles** from MSU base
- Rendezvous-- their strokes occurred median **13 miles** from base

- Time (min) from 911 alert to tPA bolus
  - 37 ± 10 with on-scene
  - 38 ± 13 with rendezvous (p=0.89)

Houston population 2,400,000
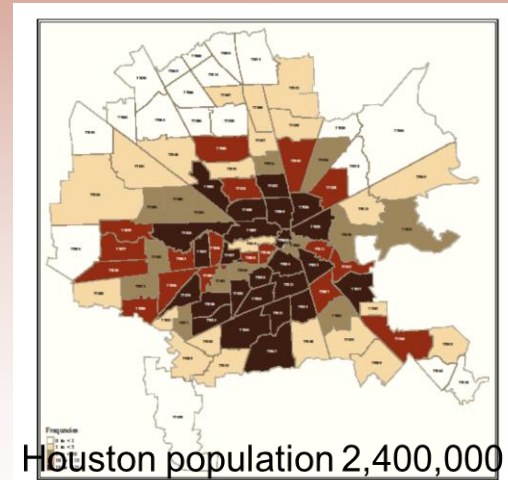
10,443 alerts

1,515 enrolled

886 enrolled MSU

629 enrolled SM

617 tPA eligible MSU

430 tPA eligible SM

3% LTFU MSU

3% LTFU SM

Assessed for eligibility
(n = 10443)

Excluded (n = 8928)
• Disregards (n = 3885)
• Stroke with exclusions (n = 2455)
• Stroke mimics (n = 2588)

Enrolled in MSU or SM
Group (n = 1515)

Allocation

Enrolled in MSU group (n = 886)

Enrolled in SM group (n = 629)

Adjudicated ineligible
for enrollment (n = 18)

Adjudicated ineligible
for enrollment (n = 5)

Adjudicated eligible for enrollment
(n = 868)

Adjudicated eligible for enrollment
(n = 624)

Adjudicated tPA
ineligible (n = 251)

Adjudicated tPA
ineligible (n = 194)

Adjudicated tPA eligible
(n = 617)

Adjudicated tPA eligible
(n = 430)

Follow-up

Lost to follow-up (n = 19)
Withdrawn (n = 6)

Lost to follow-up (n = 13)
Withdrawn (n = 4)

Analysis

Analyzed (n = 617)

Analyzed (n = 430)

Enrollment and expected enrollment of tPA-eligible patients at all sites
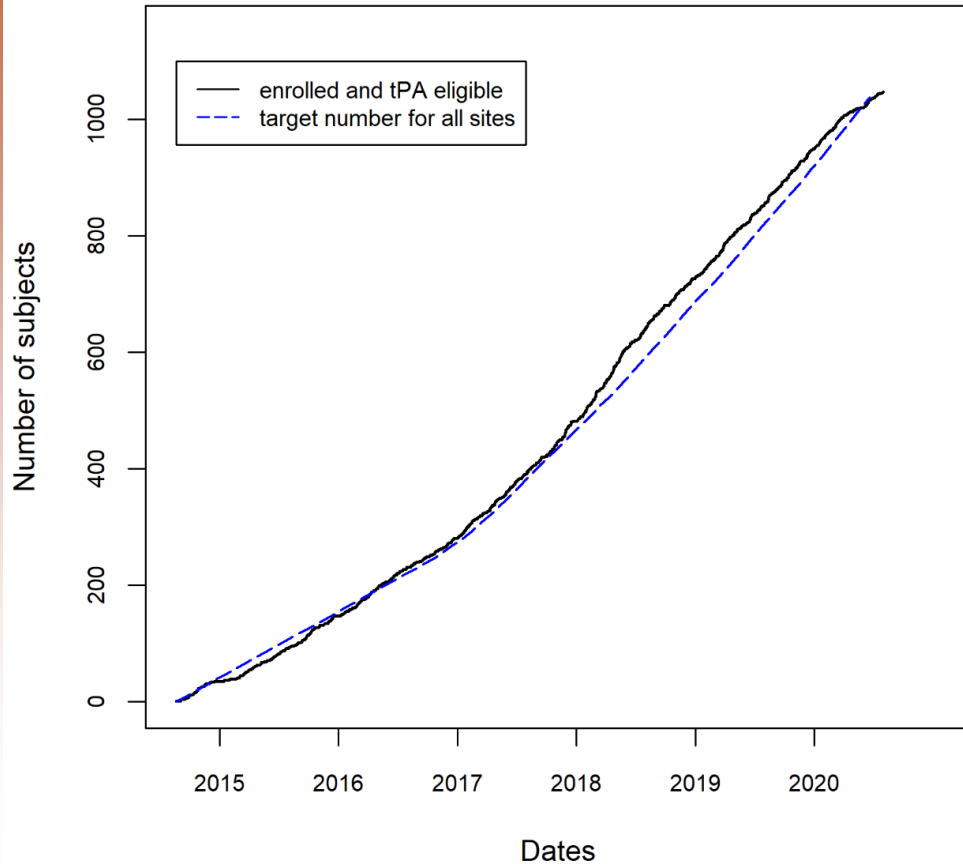
Final pt #1047 enrolled 7/31/20

Baseline Characteristics of tPA Eligible Patients

	SM (n=430)	MSU (n= 617)
Age in years, median [IQR]	65.00 [55.00, 78.00]	67.00 [57.00, 79.00]
Baseline NIHSS, median [IQR]	9.00 [6.00, 16.00]	9.00 [5.00, 16.00]
Baseline NIHSS, n (%)		
0-5	102 (23.7)	159 (25.8)
6-12	174 (40.5)	252 (40.8)
≥13	154 (35.8)	206 (33.4)
Gender		
Female, n (%)	206 (47.9)	324 (52.5)
Male, n (%)	224 (52.1)	293 (47.5)
Ethnicity		
Hispanic or Latino, n (%)	80 (18.6)	97 (15.7)
Race		
Asian, n (%)	20 (4.7)	24 (3.9)
Black or African-American, n (%)	172 (40.0)	241 (39.1)
White, n (%)	224 (52.1)	338 (54.8)
Pre-Stroke modified Rankin Scale		
0, n (%)	288 (67.0)	379 (61.4)
1, n (%)	47 (10.9)	79 (12.8)
2, n (%)	21 (4.9)	57 (9.2)
3, n (%)	58 (13.5)	74 (12.0)
4, n (%)	16 (3.7)	27 (4.4)
5, n (%)	0 (0.0)	1 (0.2)
Site		
Houston, n (%)	333 (77.4)	474 (76.8)
Colorado, n (%)	31 (7.2)	69 (11.2)
Memphis, n (%)	24 (5.6)	30 (4.9)
New York City, n (%)	11 (2.6)	17 (2.8)
Los Angeles, n (%)	17 (4.0)	6 (1.0)
Burlingame, n (%)	9 (2.1)	13 (2.1)
Indianapolis, n (%)	5 (1.2)	8 (1.3)

Final Diagnosis of tPA Eligible Patients

N (%)	MSU (N=617)	SM (N=430)
Definite stroke	420 (68.1)	311 (72.3)
Probable stroke	31 (5.0)	23 (5.3)
Stroke reversed by tPA	104 (16.9)	38 (8.8)
TIA	5 (0.8)	17 (4.0)
Stroke mimic	56 (9.1)	41 (9.5)
Missing	1 (0.2)	0 (0.0)

Time Metrics (min) in tPA Eligible Patients

	MSU Median [IQR]	SM Median [IQR]	P
LKN to tPA treatment	72 [55-105]	108 [84-147]	<0.001
EMS alert to tPA treatment	46 [39-55]	78 [66-93]	<0.001
ED door to needle	--	40 [30-51]	--
LKN to EMS alert	23 [8-52]	22 [11-60]	0.30
EMS alert to EMS arrival	9 [6-13]	9 [6-13]	0.17
EMS arrival to ED arrival	55 [47-62]	27 [21-33]	<0.001
LKN to endovascular therapy	166 [131-202]	163 [134-209]	0.76
EMS alert to endovascular therapy	141 [116-171]	132 [114-160]	0.33
ED door to endovascular therapy	76 [53-105]	94 [72-124]	<0.001

Time from LKN to tPA bolus

"Golden hour"
33% MSU
3% SM
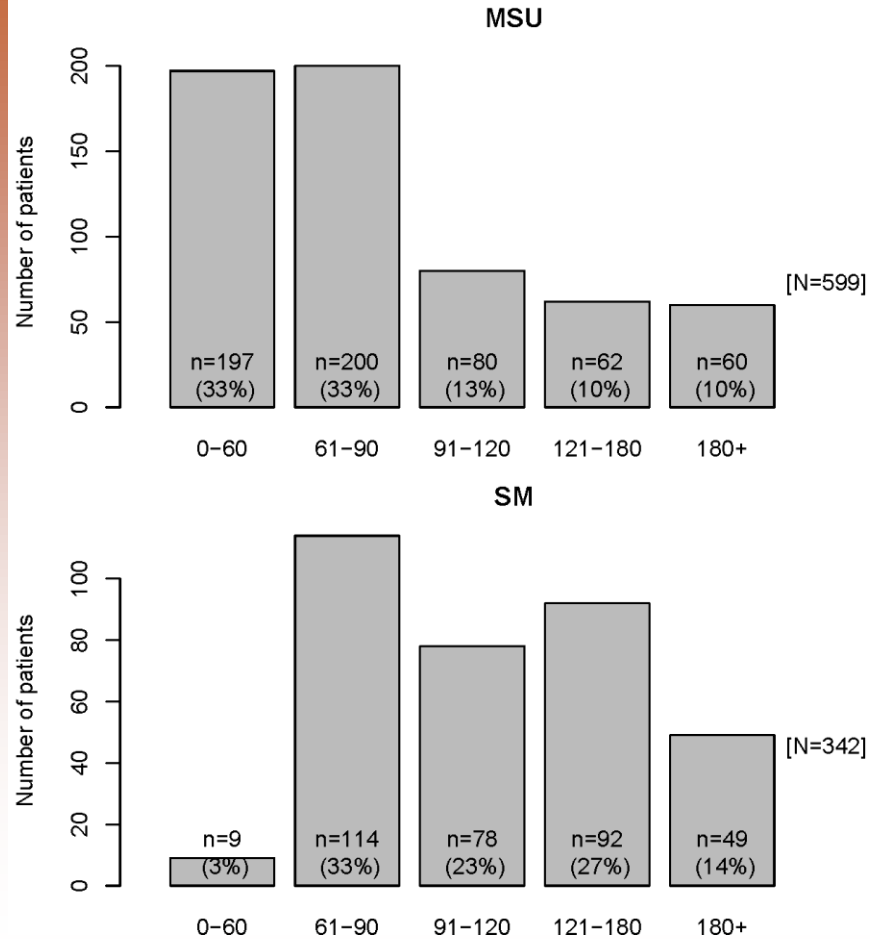
Percent of tPA Eligible Patients Treated With tPA in Each Group

	>4.5h n (%)	≤4.5h n (%)	No treatment n (%)	Total n
SM	2 (0.5)	340 (79.1)	88 (20.5)	430
MSU	0 (0.0)	599 (97.1)	18 (2.9)	617

chi-square test (p<0.001)

Primary Outcome
Distribution of uw-mRS in MSU vs SM groups

uw-mRS $\geq$ 0.91 = mRS 0,1

- MSU uw-mRS mean = 0.726
- SM uw-mRS mean = 0.657

- Difference = 0.069

p=0.002
Two sample t-test with multiple imputation

90d mRS: 0, 1, 2, 3, 4, 5, 6

MSU: 36.8 | 18.2 | 11.5 | 13.4 | 7.9 | 3.0 | 9.2

SM: 25.2 | 19.2 | 14.9 | 15.6 | 8.4 | 4.6 | 12.2

Percentage of subjects (%): 0, 25, 50, 75, 100
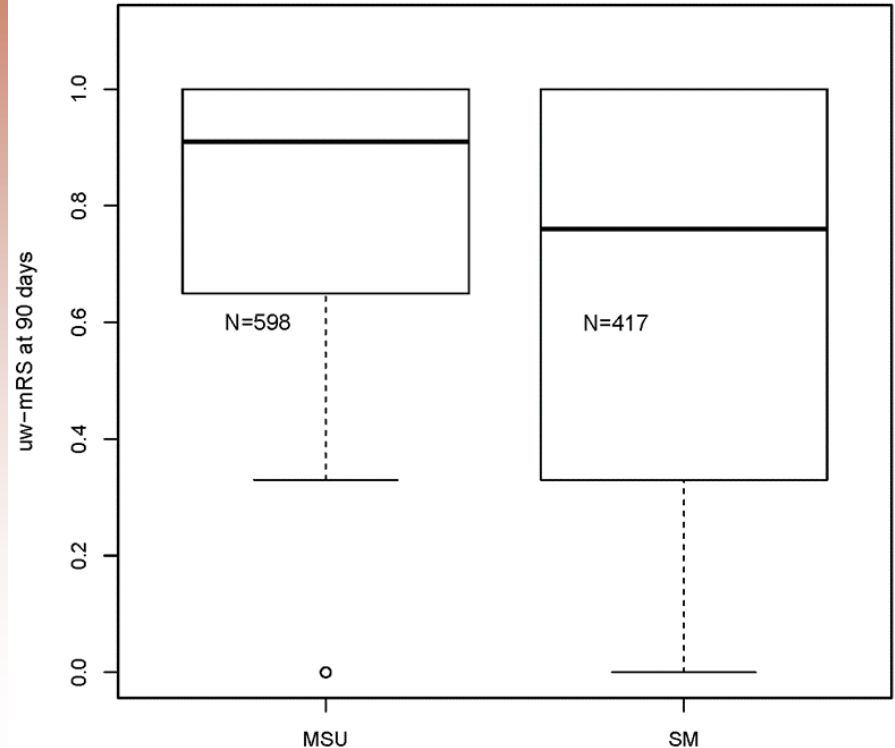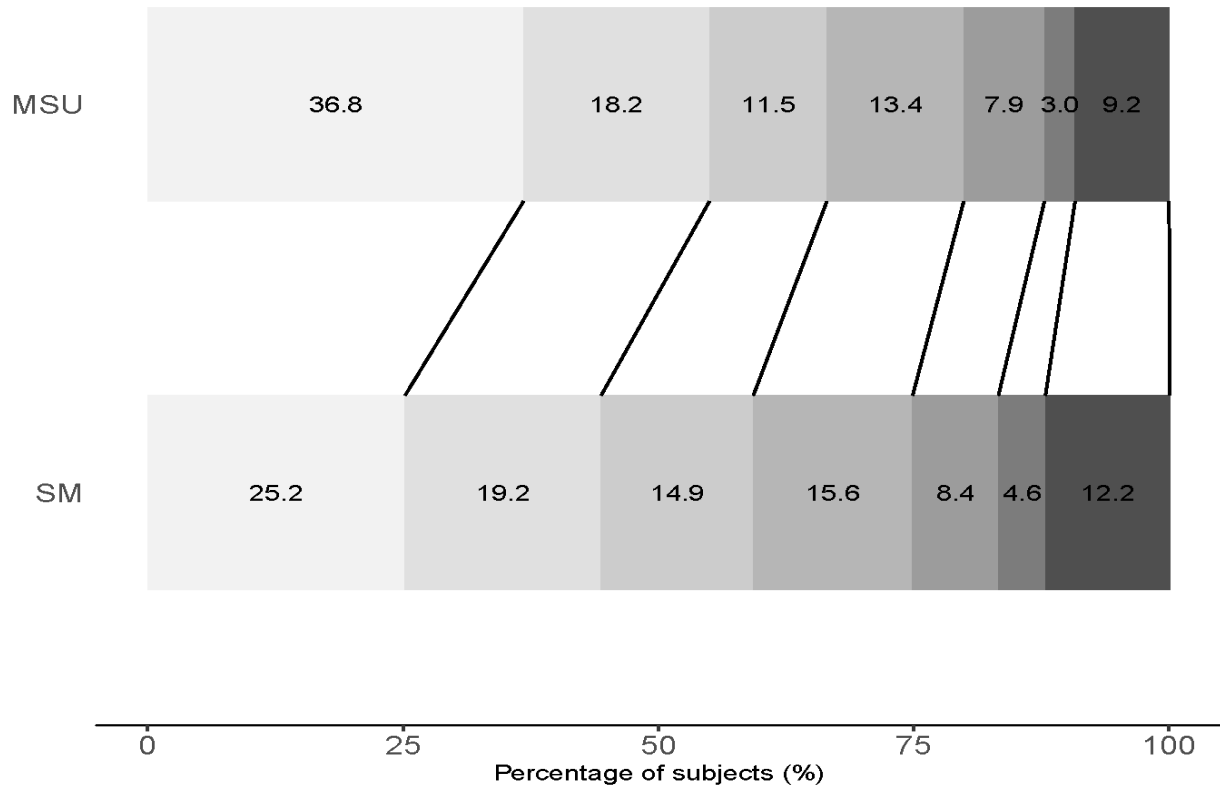
Logistic regression for mRS 0,1
OR 2.43
P <0.001

Logistic regression propensity score for mRS 0,1
OR 2.43
P <0.001

Perspective

- 0.07 difference in uw-mRS
    - c/w 0.09 difference between tPA and placebo in 0-3 hr NINDS
    - c/w 0.03 difference between tPA and placebo in 3-4.5 hr ECASS-3
    - Corroborates Berlin MSU data

- For every 100 patients treated with an MSU rather than SM,
    - 27 will have less final disability,
    - 11 more will be disability-free (mRS 0,1)

Pre-Specified Subgroups—no significant interaction

Subgroups	mRS 0-1 (MSU), n (%)	mRS 0-1 (SM), n (%)	Odds Ratio	p-value
Overall	329 (53.3)	185 (43.0)		<0.01
Sites				0.39
Houston	261 (55.1)	145 (43.5)		
Colorado	36 (52.2)	18 (58.1)		
Memphis	10 (33.3)	11 (45.8)		
New York city	10 (58.5)	4 (36.4)		
Los Angeles	2 (33.3)	5 (29.4)		
Burlingame	6 (46.2)	1 (11.1)		
Indianapolis	4 (50.0)	1 (20.0)		
LSN to EMS/MSU arrival				0.83
<= 1hr	221 (56.4)	134 (44.8)		
>1 hr	108 (48.0)	51 (38.9)		
Race				0.39
Black	128 (53.1)	62 (36.0)		
Non-Black	201 (53.5)	123 (47.7)		
Gender				0.62
Female	90 (43.7)	95 (42.4)		
Male	174 (53.7)	155 (52.9)		

Odds Ratio axis: 0.01, 0.06, 0.25, 1.00, 4.00, 16.00, 64.00, 256.00
<- Favors SM   Favors MSU ->

What about other groups (post-hoc)……?

- All definite (imaging positive) tPA-eligible ischemic strokes, excluding strokes ''reversed'' by tPA
  - OR=2.46, P<0.001

- All transported (including ICH and mimics)
  - OR 1.82; P<0.001)

- All transported <u>excluding</u> tPA-eligible or tPA-treated patients
  - NS

Therefore, positive results driven by improved outcomes in tPA treated patients,

and their benefit is great enough to produce overall MSU benefit

even if mimics, TIAs and ICH patients are transported
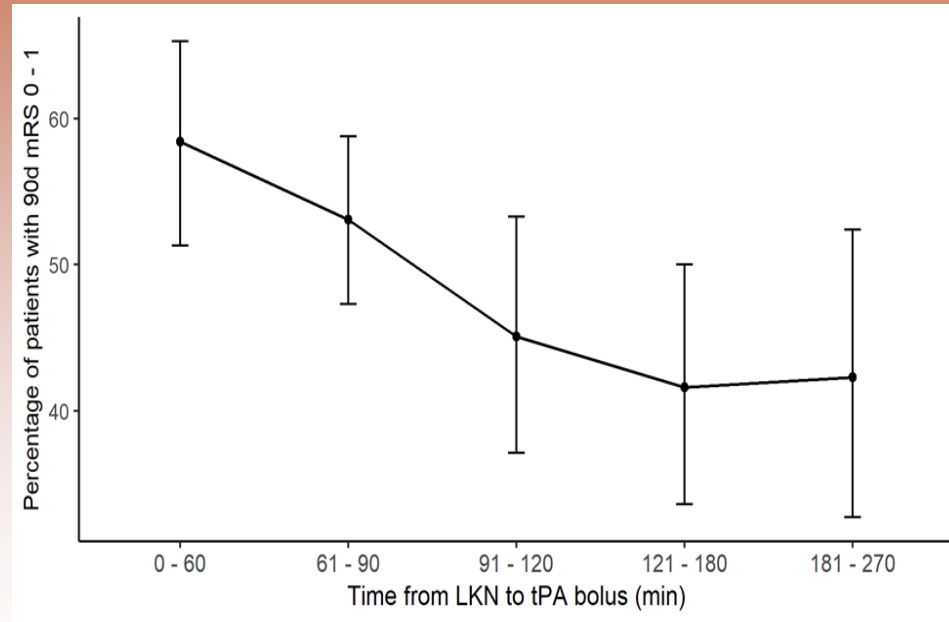
Safety

Mortality in all tPA treated pts

2% sICH in each group
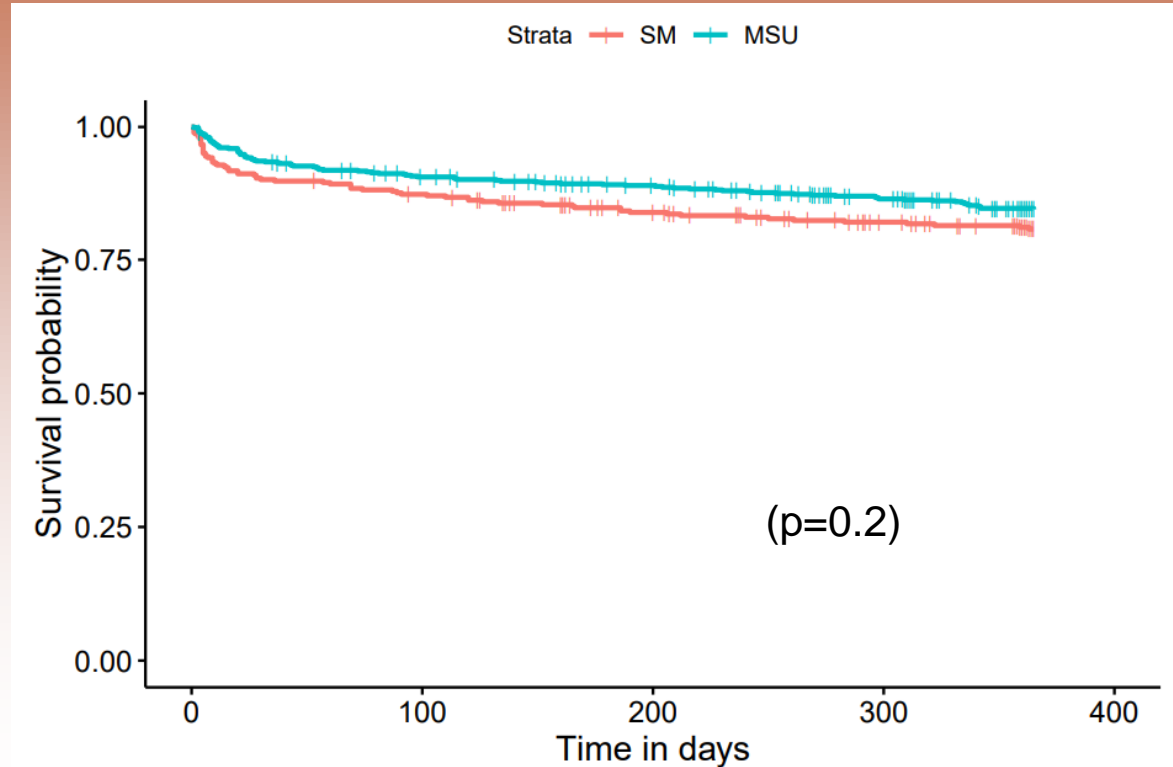
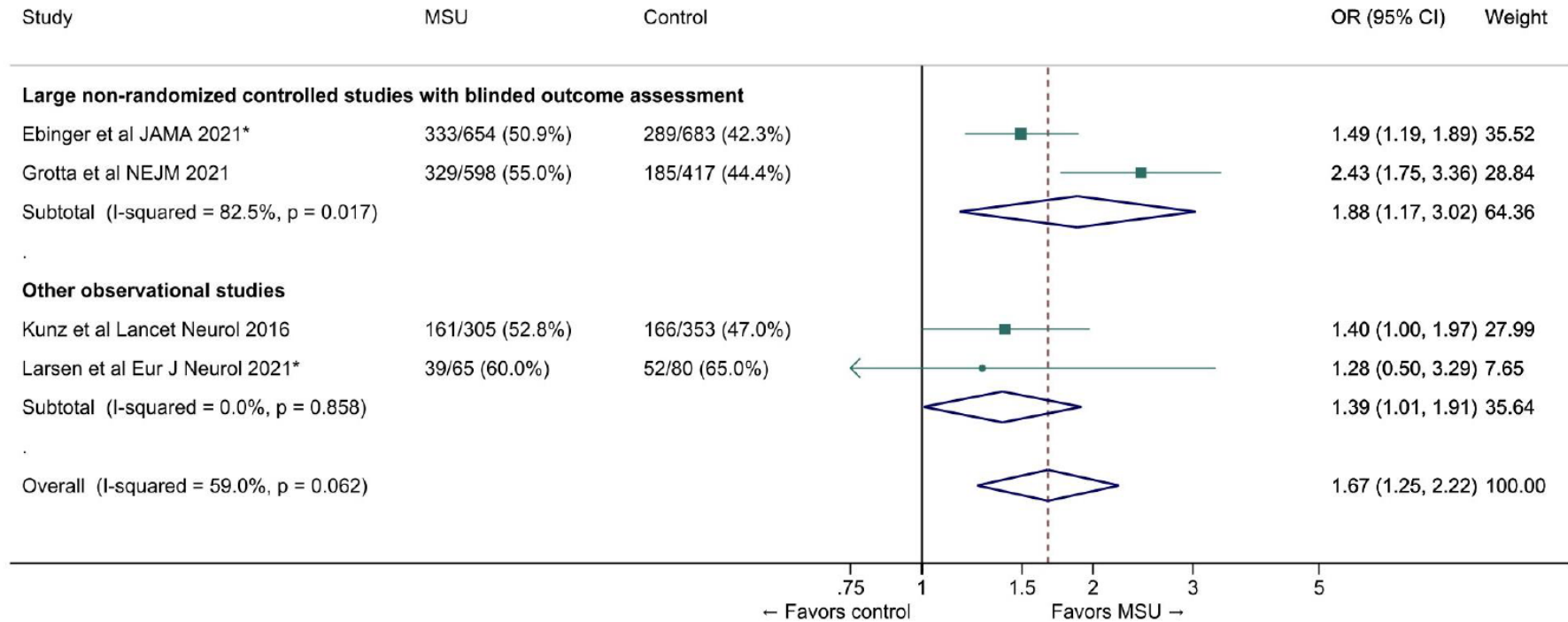# Positive Results Driven by "Golden Hour" Patients

Time from LKN to tPA bolus vs Percentage with 90d mRS 0-1
MSU + SM patients combined

Correlation between time and 90d ordinal mRS (Spearman correlation coefficient 0.15, P<0.001)
Correlation between 1hr treatment and 90d mRS 0-1 (Fisher's exact test P=0.007).

Metanalysis (submitted for publication)

Figure 2: Pooled adjusted odds ratio for excellent outcome at 90 days (mRS 0-1) in patients with MSU deployment vs. usual care (random-effects meta-analysis).

Study	MSU	Control	OR (95% CI)	Weight
Large non-randomized controlled studies with blinded outcome assessment				
Ebinger et al JAMA 2021*	333/654 (50.9%)	289/683 (42.3%)	1.49 (1.19, 1.89)	35.52
Grotta et al NEJM 2021	329/598 (55.0%)	185/417 (44.4%)	2.43 (1.75, 3.36)	28.84
Subtotal (I-squared = 82.5%, p = 0.017)			1.88 (1.17, 3.02)	64.36
Other observational studies				
Kunz et al Lancet Neurol 2016	161/305 (52.8%)	166/353 (47.0%)	1.40 (1.00, 1.97)	27.99
Larsen et al Eur J Neurol 2021*	39/65 (60.0%)	52/80 (65.0%)	1.28 (0.50, 3.29)	7.65
Subtotal (I-squared = 0.0%, p = 0.858)			1.39 (1.01, 1.91)	35.64
Overall (I-squared = 59.0%, p = 0.062)			1.67 (1.25, 2.22)	100.00

← Favors control   Favors MSU →

SA-2: Health care utilization up to 1 year post stroke

Table 37: Utilizations in time interval for all enrolled tPA-eligible (blinded review) patients

Utilization	0-3 (N=971)	4-6 (N=883)	7-9 (N=847)	10-12 (N=805)
Hospitalization				
- Yes, n (%)	225 (23.17)	132 (14.95)	110 (12.99)	95 (11.8)
- No, n (%)	744 (76.62)	744 (84.26)	735 (86.78)	706 (87.7)
- Missing, n (%)	2 (0.21)	7 (0.79)	2 (0.24)	4 (0.5)
Long-term care stay				
- Yes, n (%)	25 (2.57)	2 (0.23)	6 (0.71)	0 (0)
- No, n (%)	944 (97.22)	874 (98.98)	839 (99.06)	801 (99.5)
- Missing, n (%)	2 (0.21)	7 (0.79)	2 (0.24)	4 (0.5)
Skilled nursing facility stay				
- Yes, n (%)	139 (14.32)	17 (1.93)	9 (1.06)	9 (1.12)
- No, n (%)	830 (85.48)	859 (97.28)	835 (98.58)	791 (98.26)
- Missing, n (%)	2 (0.21)	7 (0.79)	3 (0.35)	5 (0.62)
Intermediate care NH stay				
- Yes, n (%)	29 (2.99)	19 (2.15)	9 (1.06)	8 (0.99)
- No, n (%)	940 (96.81)	857 (97.06)	835 (98.58)	792 (98.39)
- Missing, n (%)	2 (0.21)	7 (0.79)	3 (0.35)	5 (0.62)
Hospice utilization				
- Yes, n (%)	40 (4.12)	1 (0.11)	1 (0.12)	3 (0.37)
- No, n (%)	929 (95.67)	875 (99.09)	844 (99.65)	798 (99.13)
- Missing, n (%)	2 (0.21)	7 (0.79)	2 (0.24)	4 (0.5)
Emergency room visit				
- Yes, n (%)	137 (14.11)	94 (10.65)	82 (9.68)	74 (9.19)
- No, n (%)	832 (85.68)	781 (88.45)	762 (89.96)	727 (90.31)
- Missing, n (%)	2 (0.21)	8 (0.91)	3 (0.35)	4 (0.5)

SA-2: EQ5D up to 1 year post stroke

Figure 7: Mobility Problems (all enrolled tPA-eligible (blinded review) MSU and SM patients combined)
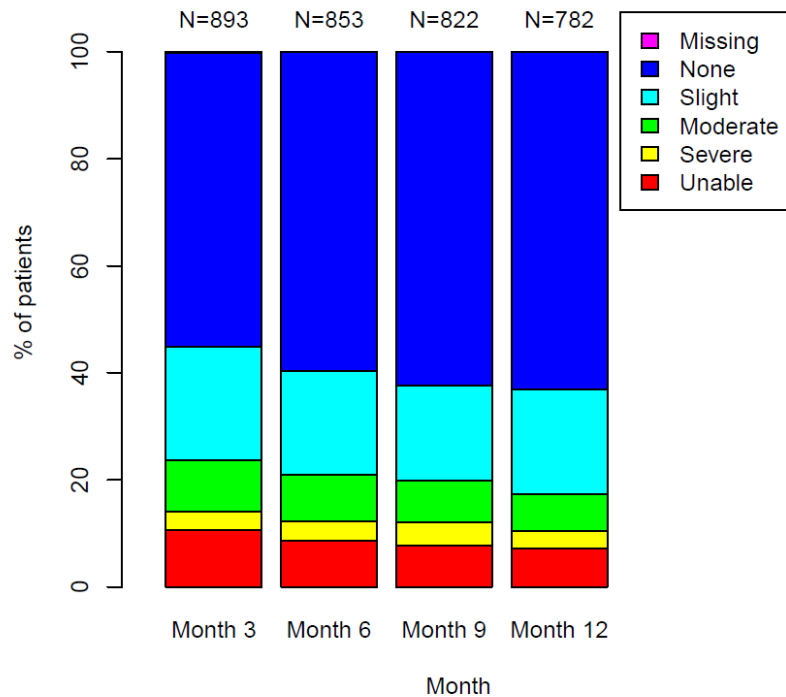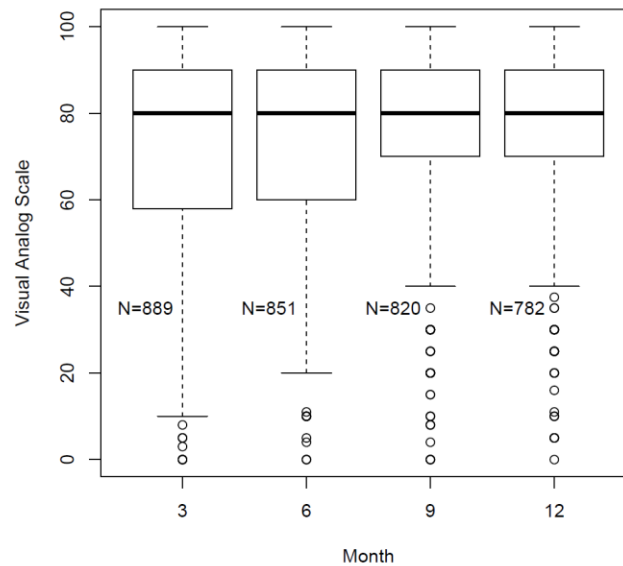
Figure 12: Distribution of Visual Analog Scale scores (all enrolled tPA-eligible (blinded review) MSU and SM patients combined)

Berlin Cost-utility (preliminary, unpublished)

3 MSU in operation + 1 back-up	MSU care €/ y
Investment (writing-off)	631,259
Maintenance	676,020
EMS staffing (including administration etc.)	660.347
Hospital staff (physicians and technicians) + teleradiology + medical quality management	1,931,666
Medication and medical equipment	352.134
Savings of hospital costs	-414.685
Savings by avoidance of additional EMS dispatches (emergency physicians, helicopters)	-382.039
Savings by reduced long-term care	-295,204
Total costs for 3 MSU stroke care / y	**3.160.246**

With 75 quality adjusted life years (QALY) saved per year:

Adjusted incremental costs per QALY: €41.011

Arresting early hematoma growth with quicker hemostatic therapy
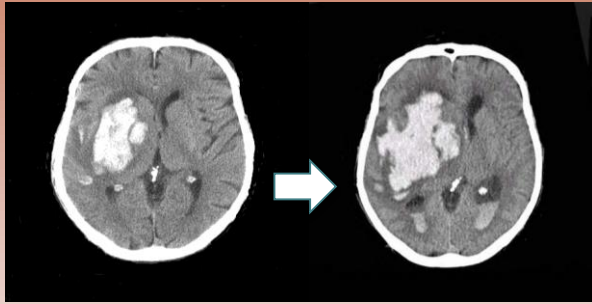
FASTEST STUDY
- rFVIIa
- **< 2 hrs from onset**
- **ICH $\geq$ 2 and < 60 cc**
- 860 pts
- NIH Stroke Net
- **EFIC**
- **At least 15 international MSUs**

Next Steps

1. Complete prospective health utilities and QOL analysis

2. Approach payers with data for appropriate reimbursement

3. Updating of practice guideline statements to reflect new efficacy data

4. Inclusion of MSUs in pre-hospital matrix for stroke centers

5. Additional areas of clinical research
    1. Clinical trials of new stroke treatments—fVIIa for ICH, TNK
    2. Speeding EVT
    3. Validation of newer diagnostic modalities—biomarkers, LVO or blood detection
    4. Additional studies in rural/underserved populations
    5. Implementation research– earlier alerting, more accurate triage, better coordination with EMS and destination hospitals
    6. Shared registry database among global MSUs—PRESTO
    7. Application to other diseases—cardiac arrest, head trauma

Conclusions…. BEST-MSU Study

- Groups balanced; diverse population from 7 sites
- Only 3% lost to follow-up
- Completed on schedule despite COVID
- Results were robust to the various statistical methods, all outcomes, and sensitivity analyses.
- MSU management c/w Standard:
    - 17% more treated with tPA (97% vs 80%)
    - 30% more treated within first "golden hour" from LKN (33% vs 3%)
    - Significantly improved patient-centered outcomes (p=0.002)
    - 10% more with mRS 0,1 at 90 days (53% vs 43%) (p< 0.001)
    - Results also positive if including all 1515 enrolled (transported) pts
    - No safety issues…9% mimics and 2% sICH in each group
- 1 year f/u for health care utilization and QOL ongoing