



Stanford
MEDICINE



defuse · 3



- 1990s - DWI estimates ischemic core; perfusion imaging estimates critically hypoperfused tissue
- 2006 - DEFUSE: MR Target mismatch profile identifies patients who respond favorably to late window thrombolysis
- 2008 - RAPID software: Automated processing of advanced imaging data to estimate the volume of salvageable tissue
- 2012, 2016 - DEFUSE 2 / CRISP: MR/CT Perfusion target mismatch respond favorably to late window thrombectomy

- DEFUSE 3 Investigators and coordinators
- 296 patients and family members who signed consent form
- StrokeNet, for unique infrastructure
- NIH, for funding all 3 DEFUSE studies
- iSchemaView, for RAPID software platform
- DEFUSE 3 Executive and Endovascular Committees, DSMB, Statisticians, Medical Monitor, Imaging Core Lab, Central IRB
- DEFUSE Research Manager, Stephanie Kemp

- Hypothesis: Stroke patients with MCA and/or ICA occlusion and salvageable tissue identified by CT/MR perfusion benefit from endovascular thrombectomy between 6-16 h.
- Design: Eligible patients randomized to thrombectomy (FDA cleared device) vs. medical management alone
- Endpoint: Modified Rankin Scale, blinded assessor, day 90 Primary: ordinal shift analysis; Secondary: mRS 0-2

Key Clinical Inclusion Criteria

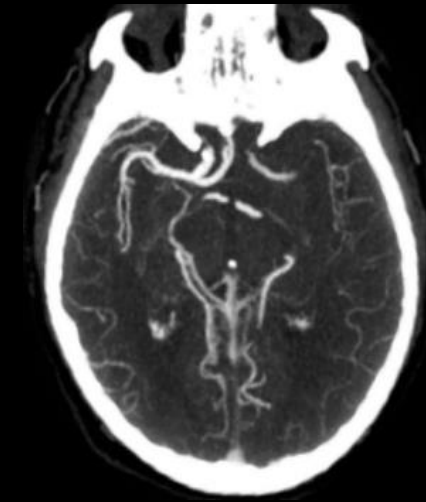
Age	18 - 90 years
NIHSS	≥ 6
Pre-stroke mRS	0 - 2
Femoral puncture	6 - 16 hours

Key Neuroimaging Inclusion Criteria

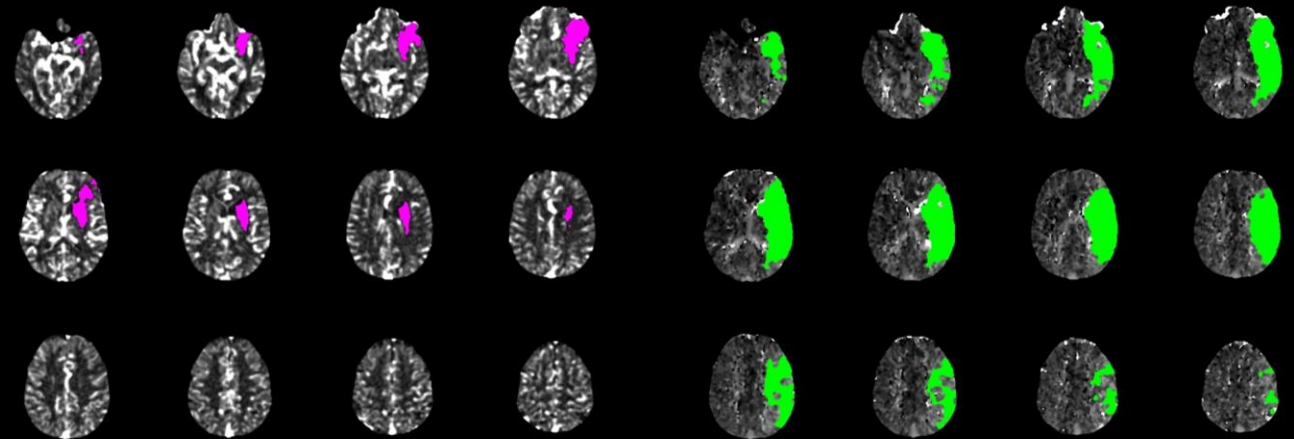
1) Occlusion of the ICA and/or MCA M1

AND

2) **RAPID** Target Mismatch Profile
with core up to 70 ml



Substantially more
patients eligible



CBF<30% volume: 26 ml

Tmax>6.0s volume: 167 ml

Mismatch volume: 141 ml

Mismatch ratio: 6.4

Early Termination

- A similar late-window study, DAWN, reported positive results in May 2017
- DEFUSE 3 was placed on hold for an early interim analysis
- Following this analysis, $N = 182$, the study was ended

Patient Accrual

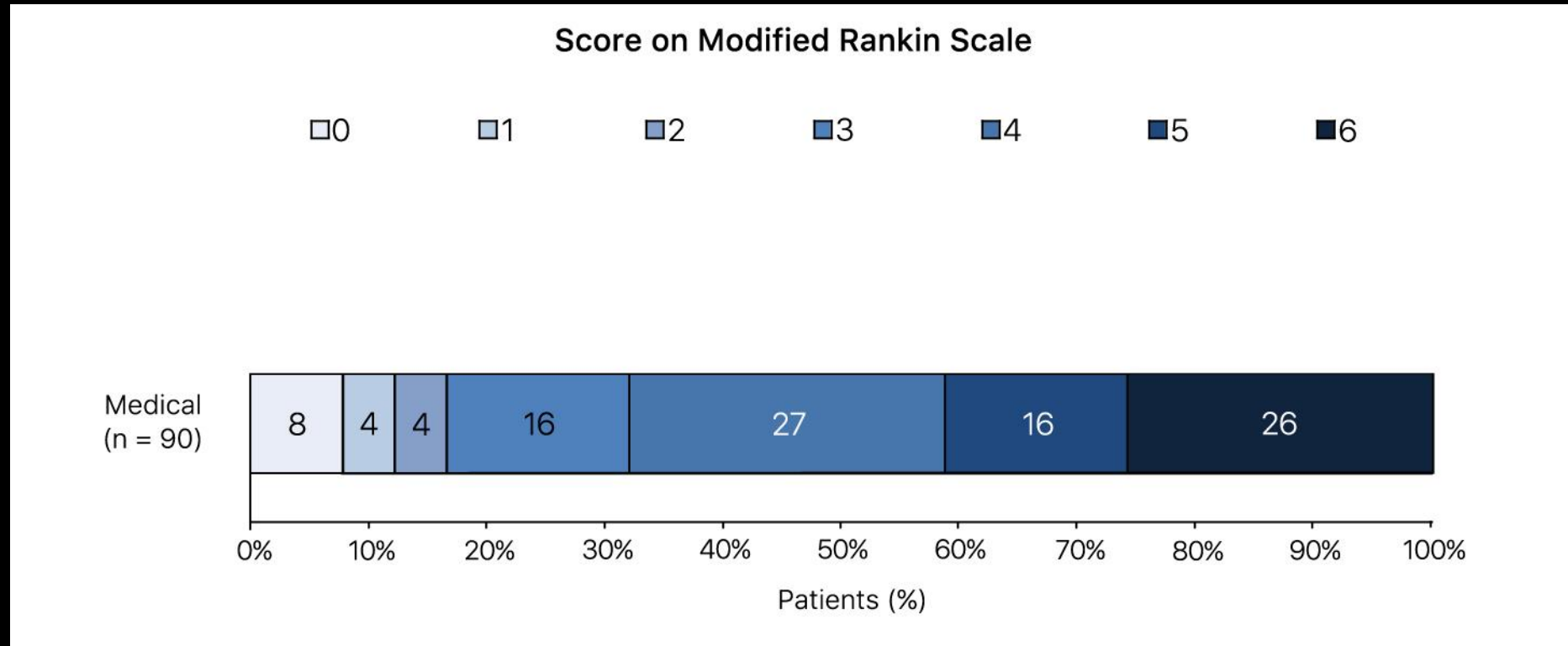


- 182 patients randomized in 1 yr at 38 sites
- Enrollment rate nearly double projected target
- Substantially faster than prior trials

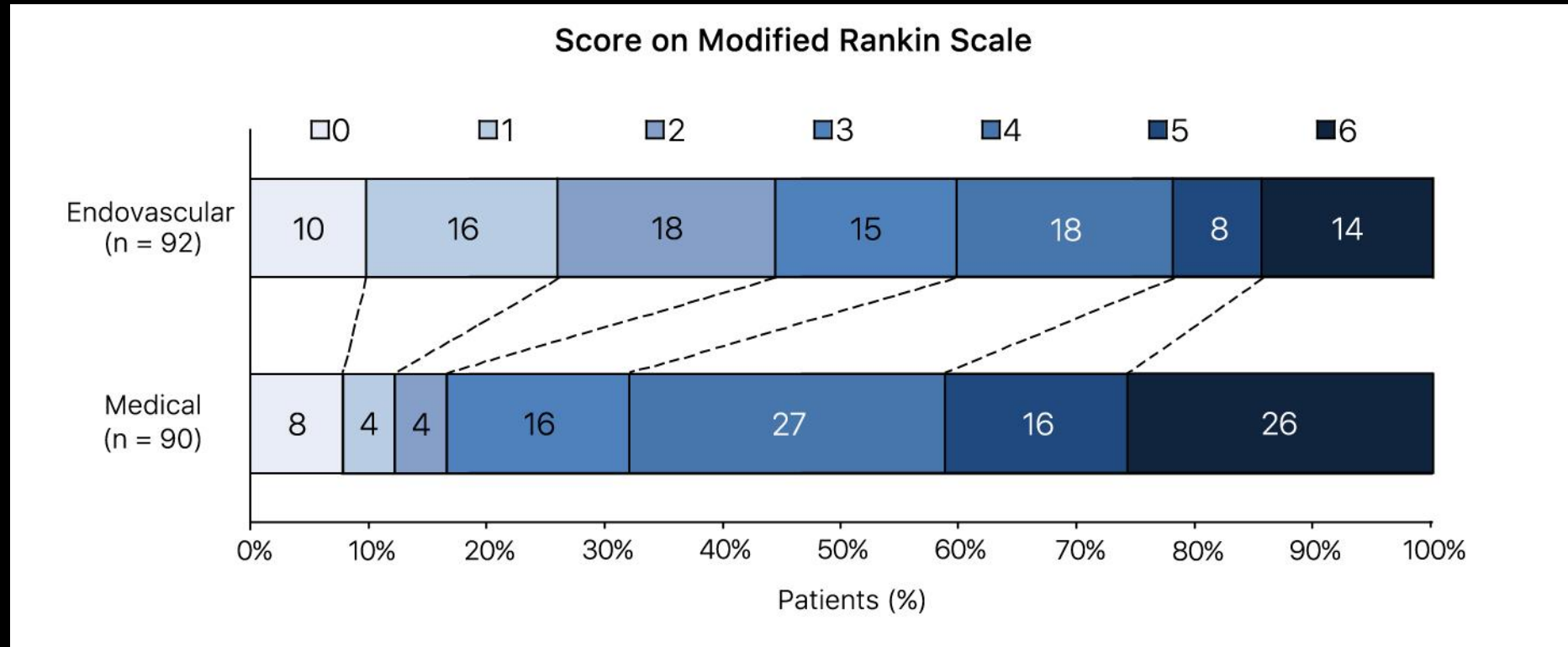
Baseline Characteristics

	Endovascular (N = 92)	Medical (N = 90)
Age, yr - median (IQR)	70 (59 - 78.5)	71 (59 - 80)
NIHSS score - median (IQR)	16 (10 - 20)	16 (12 - 21)
Stroke onset to randomization - median (IQR)	10:53 (8:46-12:21)	10:44 (8:42-13:04)
Stroke onset wake-up (%)	53%	47%
Treatment with intravenous tPA (%)	11%	9%
Qualifying imaging: CT Perfusion	75%	71%
Ischemic core volume, ml - median (IQR)	9 (2 - 26)	10 (2 - 24)
Perfusion lesion (Tmax>6s) volume, ml - median (IQR)	115 (79-146)	116 (73 - 158)
Middle cerebral artery occlusion on baseline CTA / MRA	65%	60%

Results: Primary Outcome



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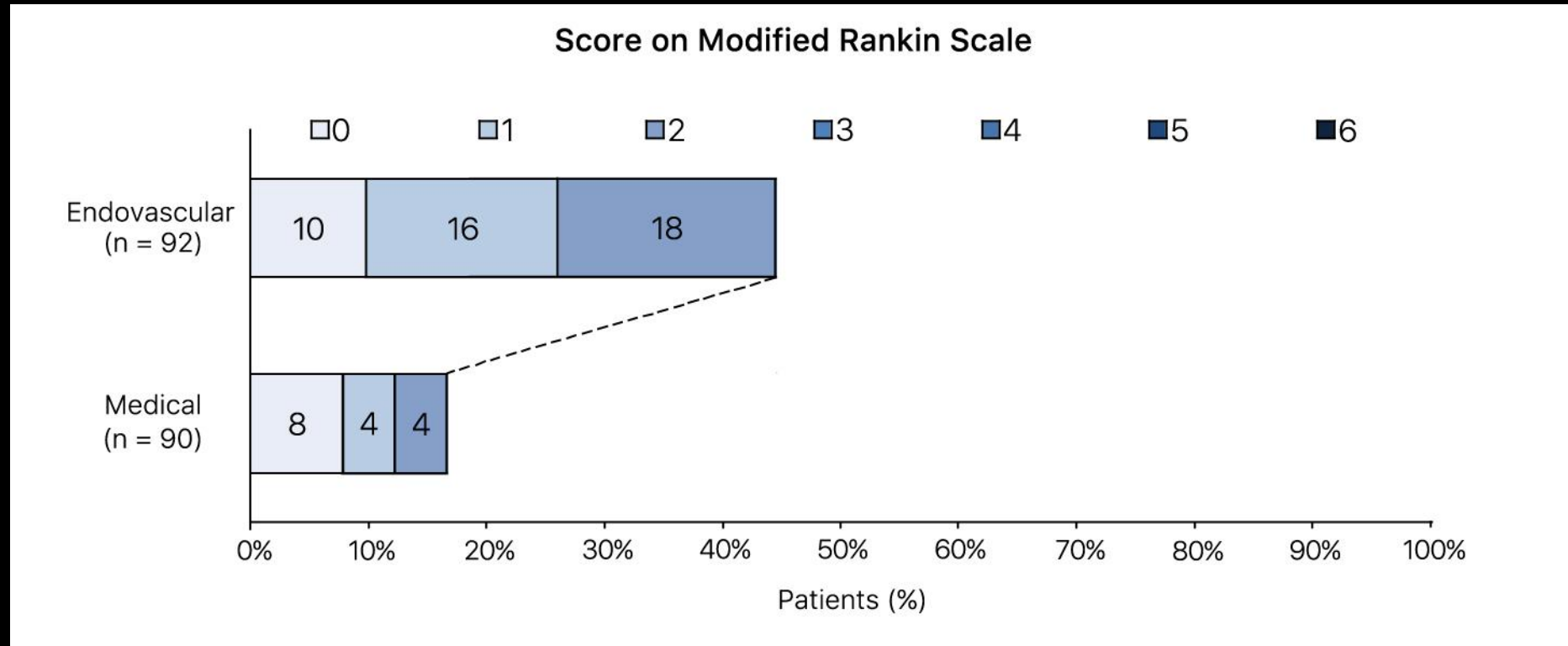


Odds ratio: 2.8 (1.6 - 4.7) $P < 0.0001$

Adjusted odds ratio: 3.4 (2.0 - 5.8) $P = 0.0004$

Number needed to treat: 2

Secondary Outcome (mRS 0-2)

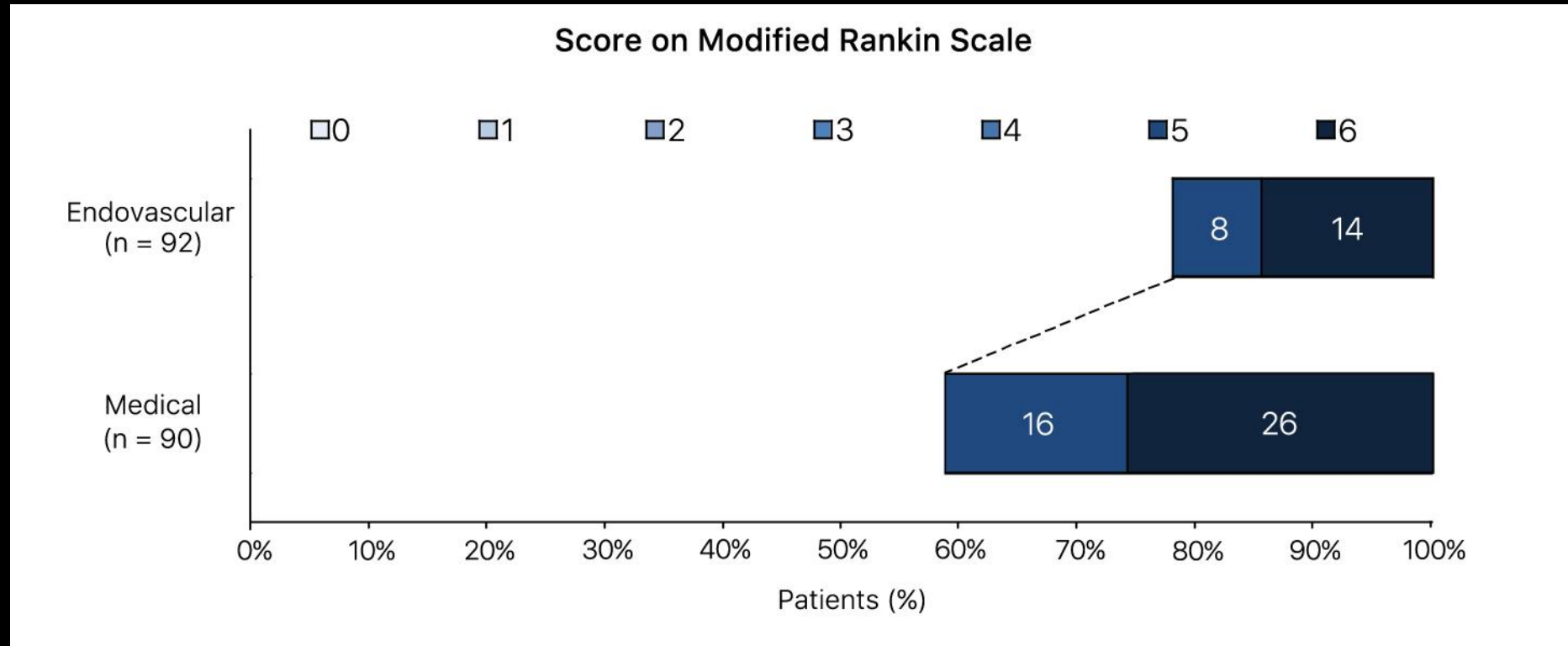


mRS 0-2

45% vs. 17%

$P < 0.0001$

Severe disability/death (mRS 5-6)



mRS 5-6

22% vs. 42%

P=0.0048

Reperfusion and Recanalization

	Endovascular	Medical	P-value
Reperfusion*	79%	18%	<0.0001
Recanalization**	78%	18%	<0.0001

* >90% reduction in the Tmax>6s perfusion lesion at 24 h

** complete recanalization on MRA/CTA at 24 h

Primary Safety Outcomes

	Endovascular	Medical	P-value
Symptomatic ICH*	6.5%	4.4%	0.75

* 5/6 patients with SICH died in endovascular vs. 2/4 in medical

Primary Safety Outcomes

	Endovascular	Medical	P-value
Symptomatic ICH*	6.5%	4.4%	0.75
Death	14%	26%	0.05

DAWN Eligibility

	Treatment effect mRS shift, OR (95% CI)
DAWN-eligible*	2.7 (1.4 - 5.2)
DAWN ineligible	3.0 (1.3 - 7.0)

*62% of DEFUSE 3 patients met DAWN eligibility criteria

Wake-up vs. Witnessed onset

	Treatment effect mRS shift, OR (95% CI)
Wake-up	3.4 (1.6 – 7.4)
Witnessed onset*	3.4 (1.4 – 8.3)

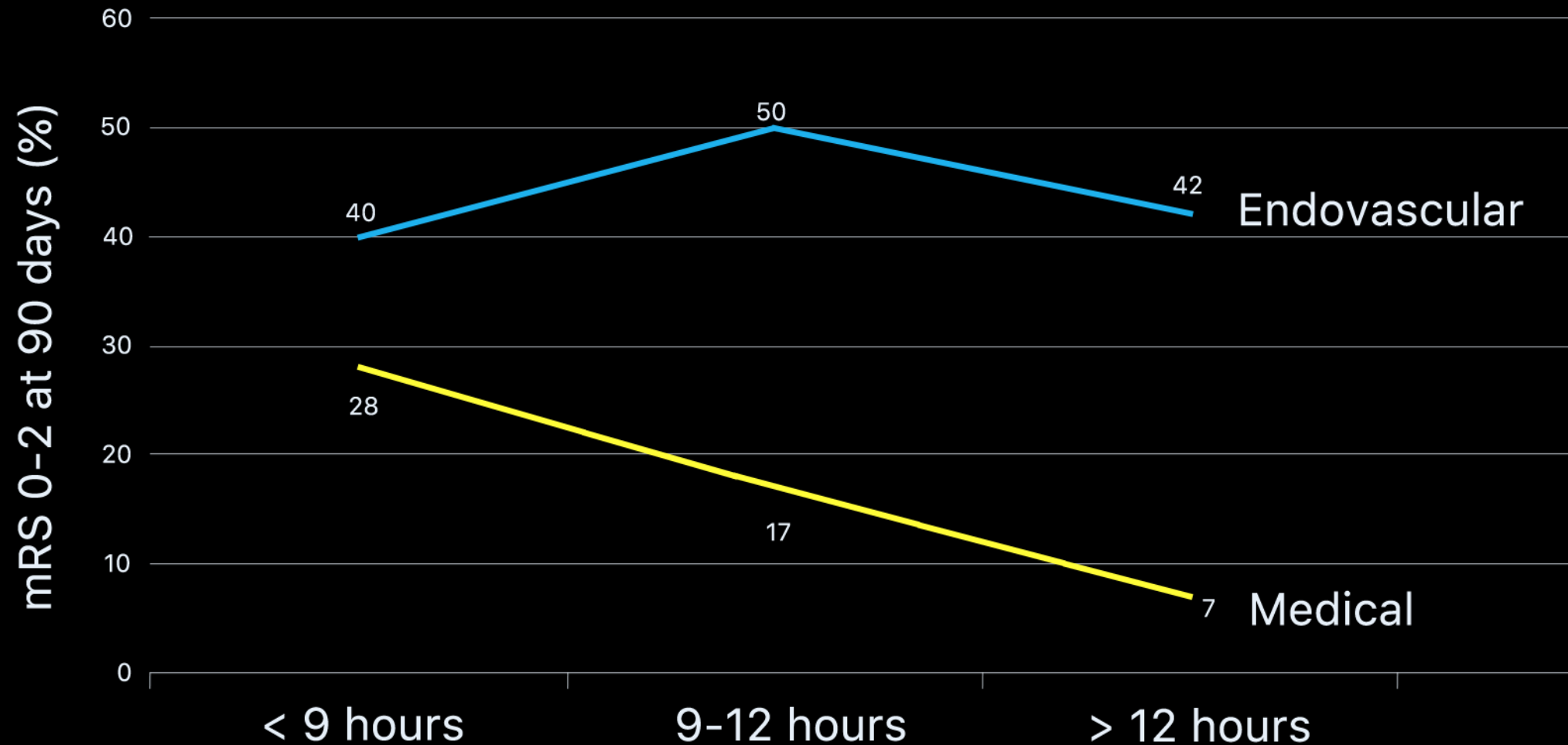
*Median time to randomization 9.5 hours

Time to Randomization

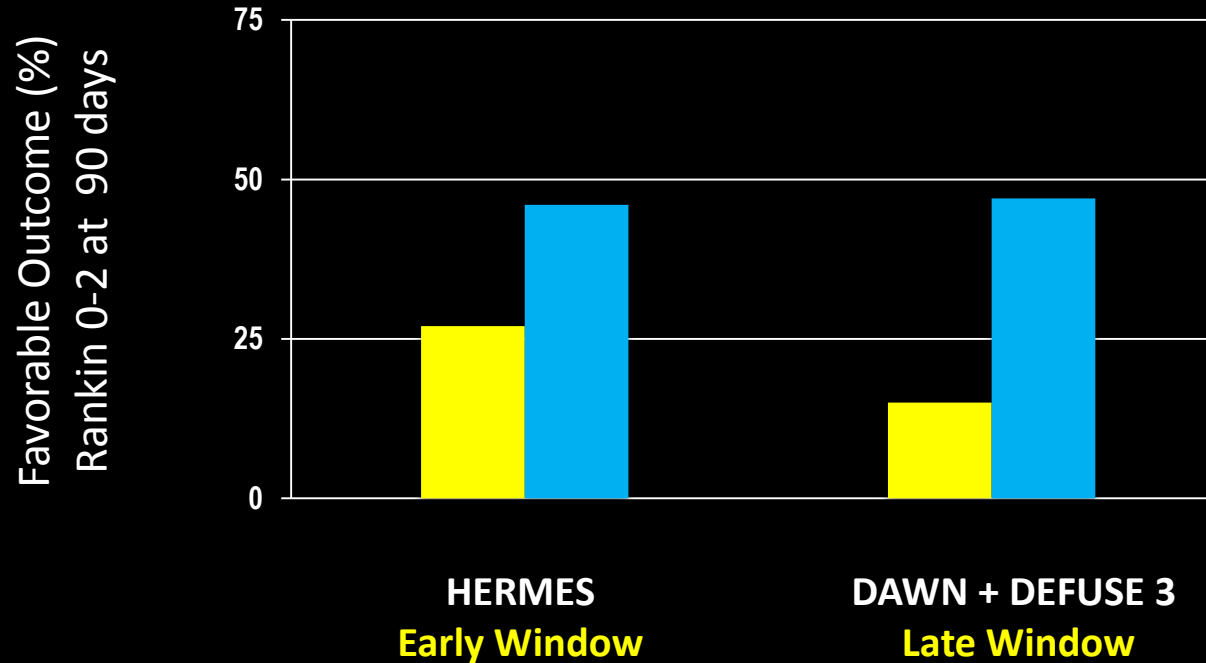
	Treatment effect mRS shift, OR (95% CI)
Randomized > 11 h	5.7 (2.4 – 13.1)
Randomized \leq 11 h*	1.7 (0.9 – 3.4)

*P-value for interaction = 0.07

Functional Outcome (mRS 0-2) at 90 days: Time from Symptom Onset to Randomization



Late Window Paradox



Endovascular

46%

47%

Control

27%

15%

P = 0.006 for difference
in treatment effect

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

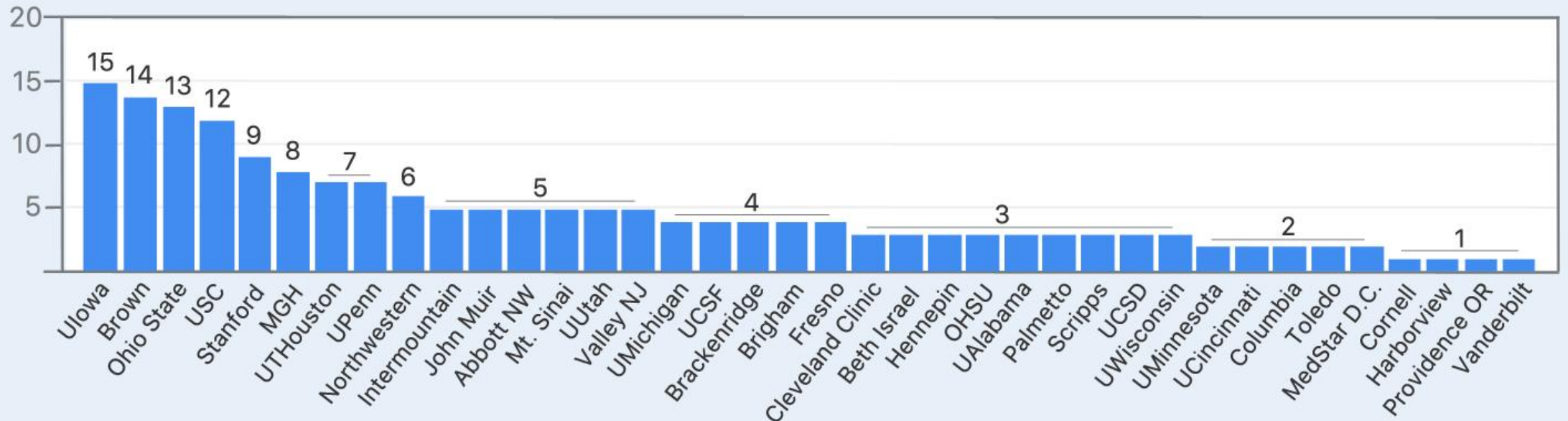
DEFUSE 3 Investigators, NEJM, Jan 24, 2018

- DEFUSE 3 extends late window therapy to larger population identified by CT perfusion or diffusion/perfusion mismatch
- Considerable clinical benefit across the disability spectrum
- Immediate impact on treatment guidelines
- Substantial effect on stroke imaging, triage and treatment
- New perspective on “time is brain”



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DEFUSE 3: Enrollment By Site



40 sites activated; 38 enrolled

0 sites withdrawn