Update on Treatment of Acute Ischemic Stroke

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Presenter Disclosure Information

Toby Gropen, MD, FAHA
Update on Treatment of Acute Ischemic Stroke

FINANCIAL DISCLOSURE:
None

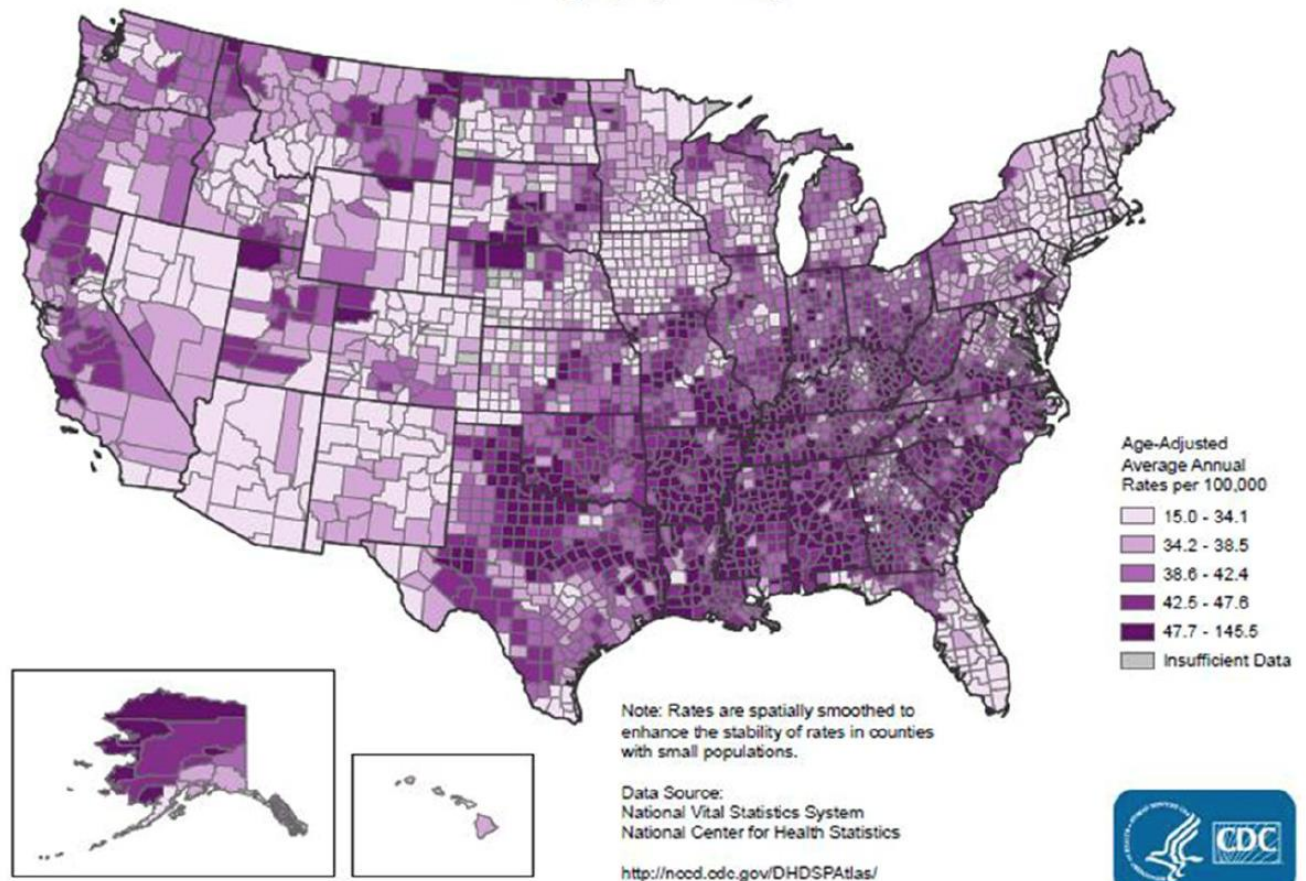## UNLABELED/UNAPPROVED USES DISCLOSURE:
None

OBJECTIVES

- Appreciate morbidity and mortality associated with large-vessel occlusive stroke (LVO)
- Review use and limitations of intravenous thrombolysis for LVO
- Discuss new literature supporting endovascular treatment of stroke
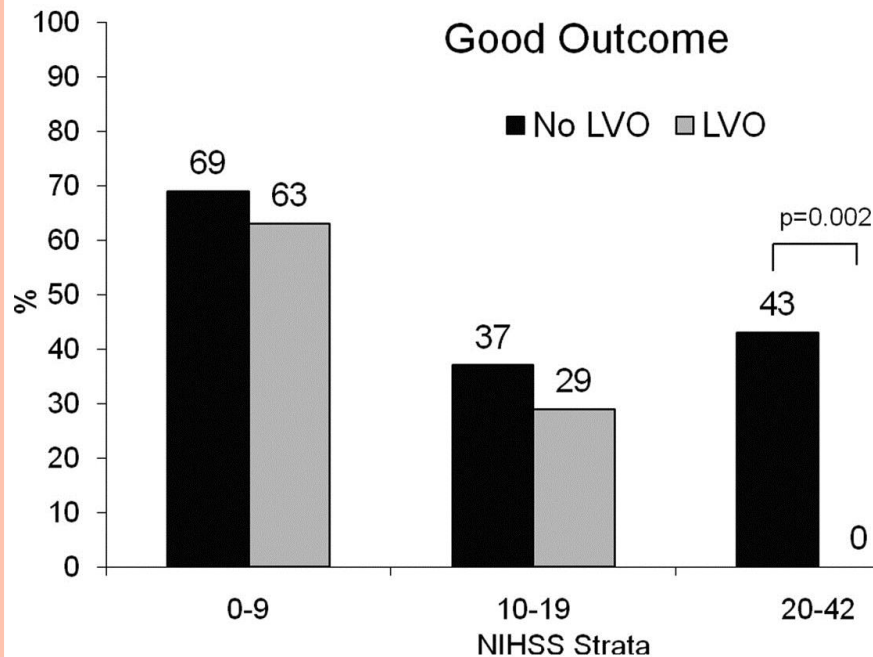- Describe patient selection for interventional stroke procedures

ALABAMA IS #1!

FIGURE 1

Stroke Death Rates, 2011-2013
All Ages, by County

Age-Adjusted
Average Annual
Rates per 100,000

- 15.0 - 34.1
- 34.2 - 38.5
- 38.6 - 42.4
- 42.5 - 47.6
- 47.7 - 145.5
- Insufficient Data

Note: Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics

http://nccd.cdc.gov/DHDSPAtlas/

CDC

OUTCOME RELATED TO LVO: STOP STROKE STUDY

mRS ≤ 2 (OR, 0.33; 0.24 to 0.45; $P<0.001$)
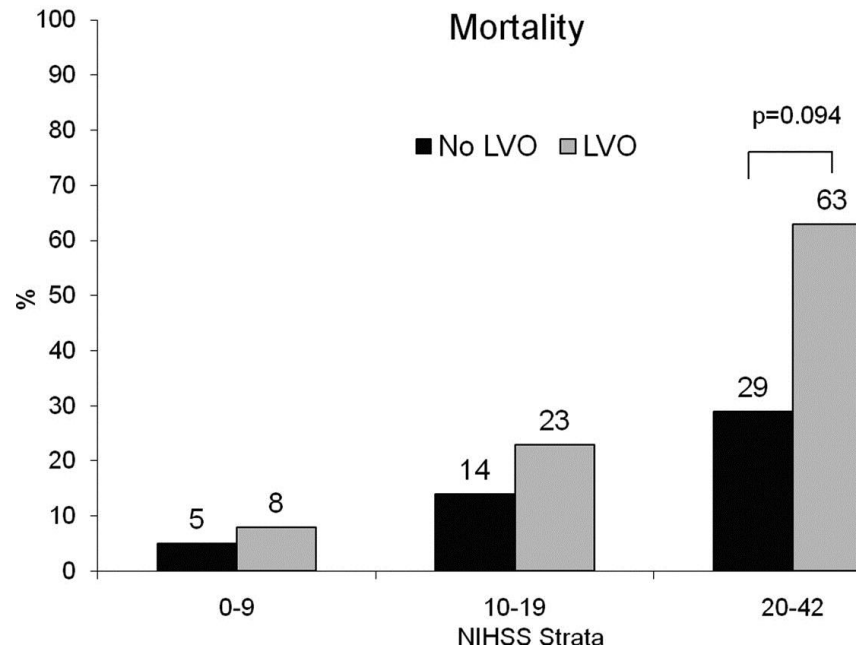
6-month mortality (OR, 4.5; 95% CI, 2.7 to 7.3; $P<0.001$)

Smith, 2009

EVERY SECOND COUNTS!

Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/218 yards	8.7 h

Saver, 2006

BENEFIT AND HARM OF T-PA PER 100 PATIENTS

Lansberg, 2009
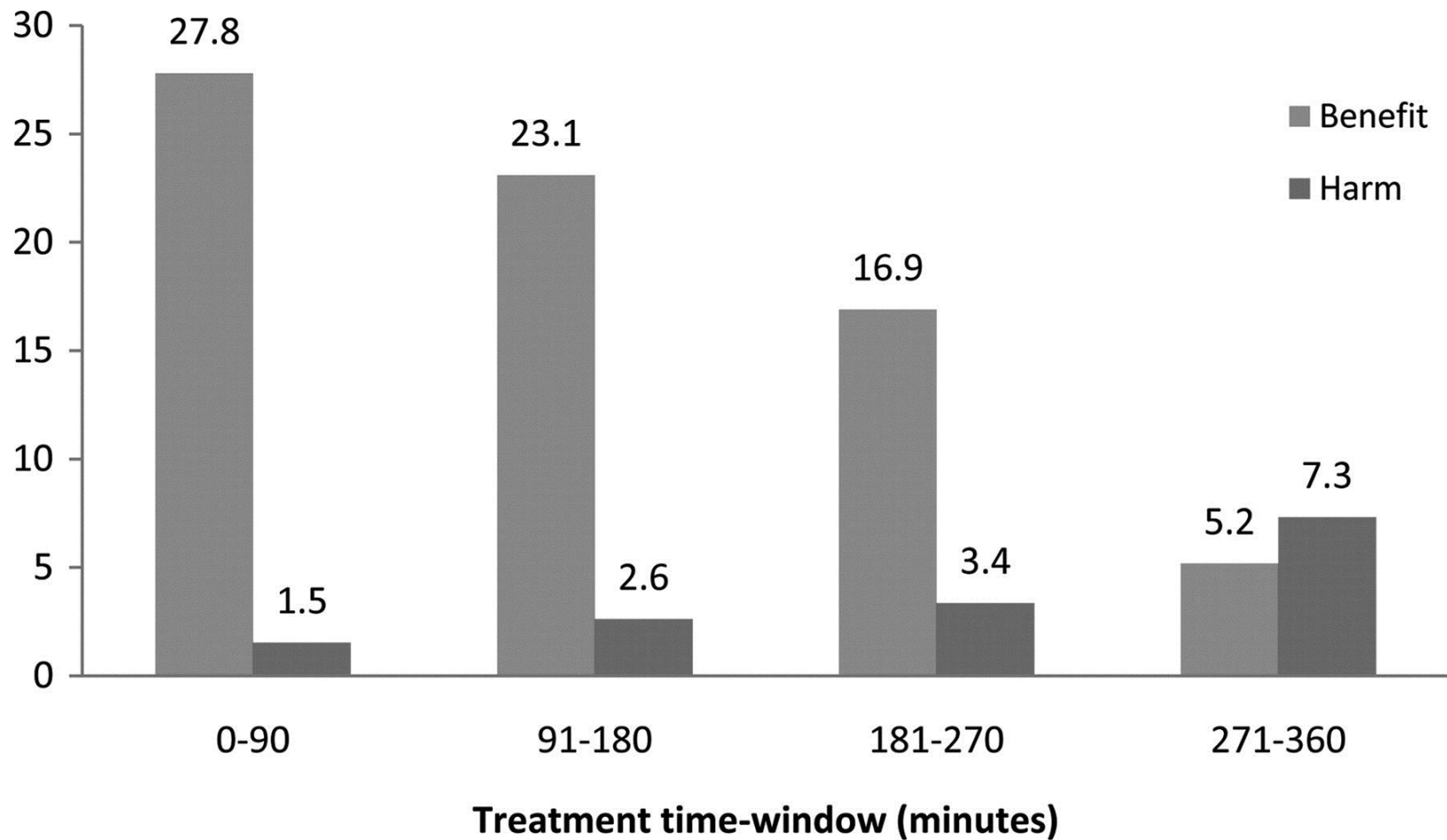
RECANALIZATION WITH T-PA AND THROMBUS LENGTH

Riedel, 2011
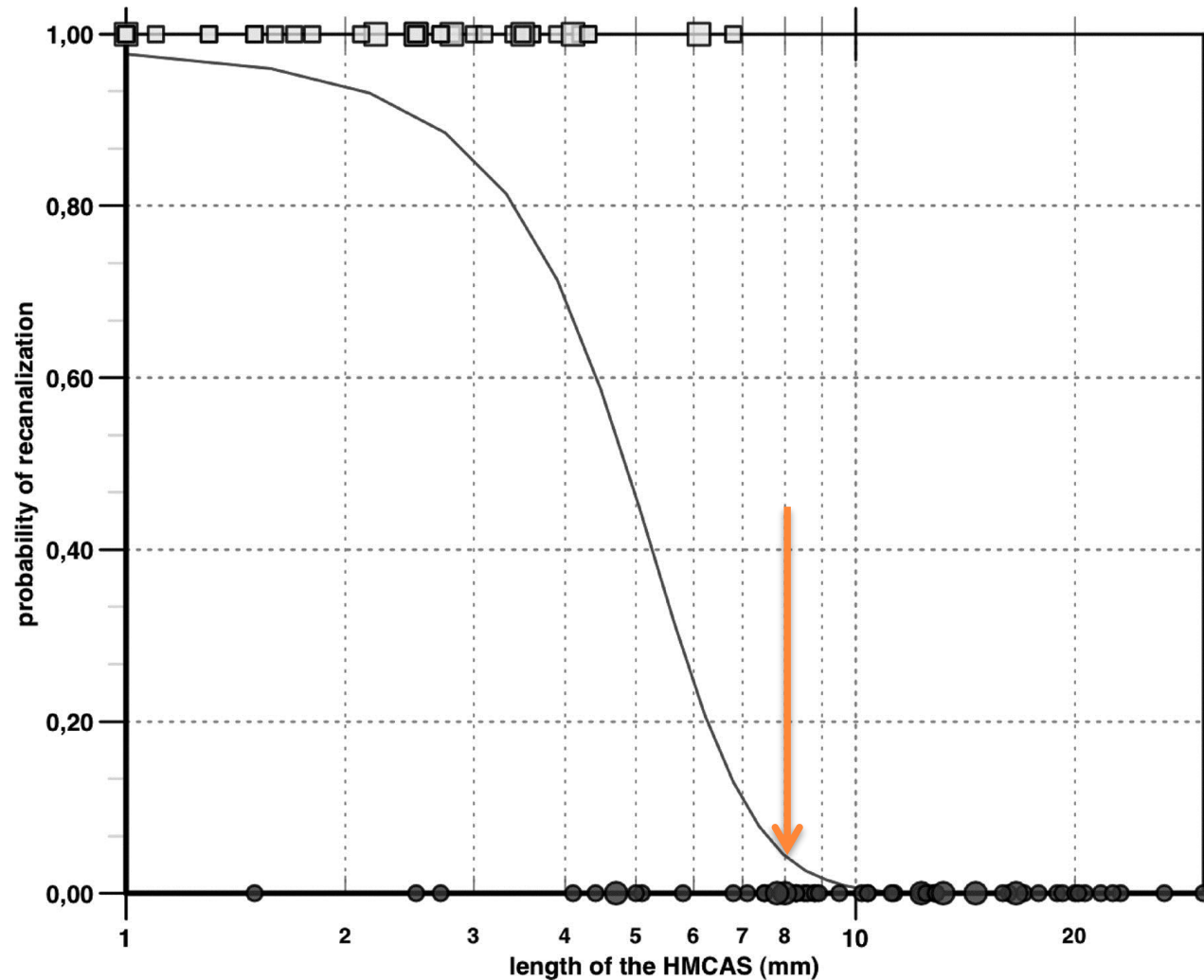
RECANALIZATION AND TREATMENT METHOD

Rha, 2007
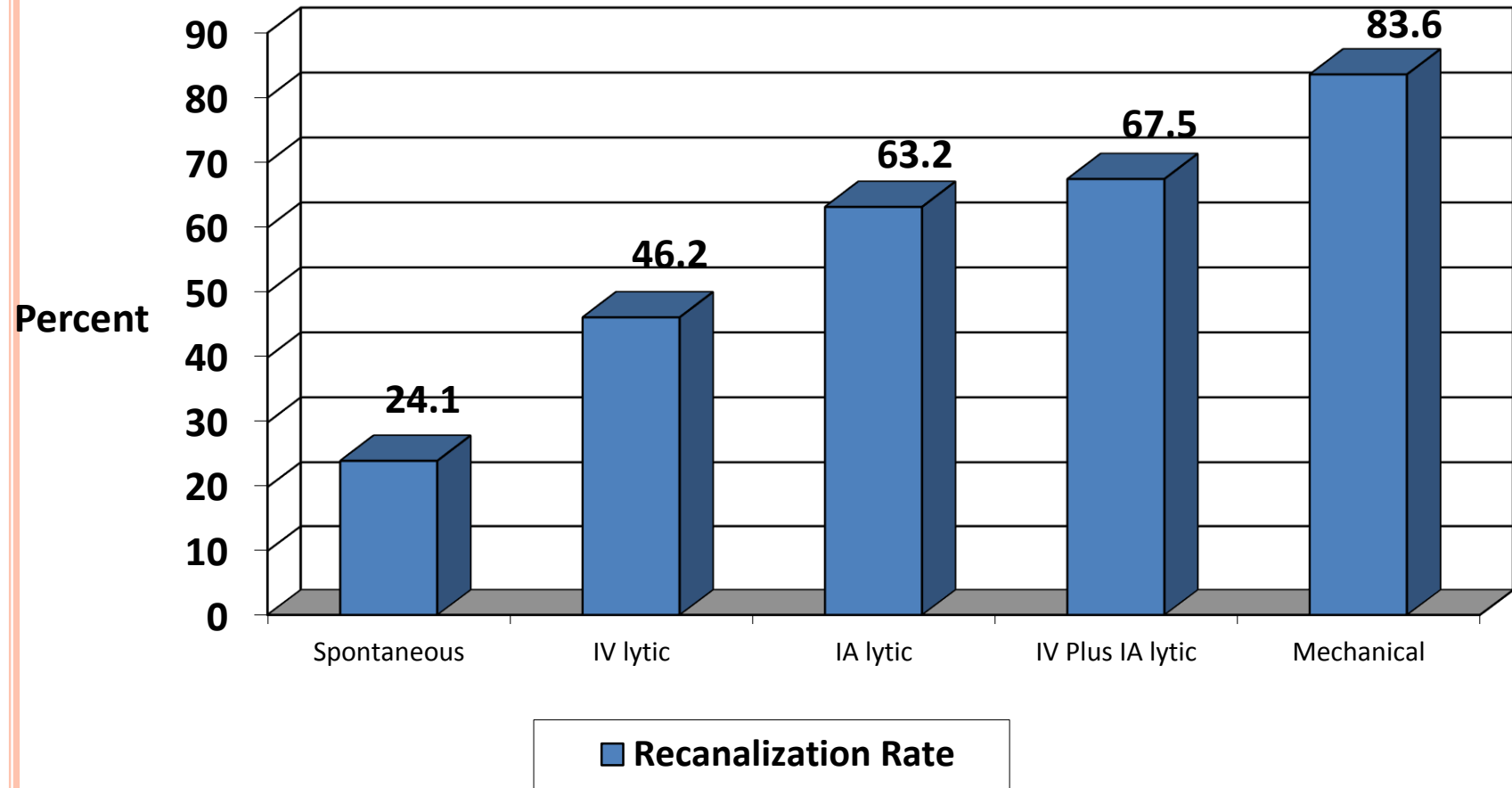
MR CLEAN METHODS

- AIS caused by a proximal intracranial arterial occlusion (ICA, M1, M2, A1, A2)
- 18 years of age or older
- NIHSS ≥ 2
- Initiation of MT < 6 hours after LKW
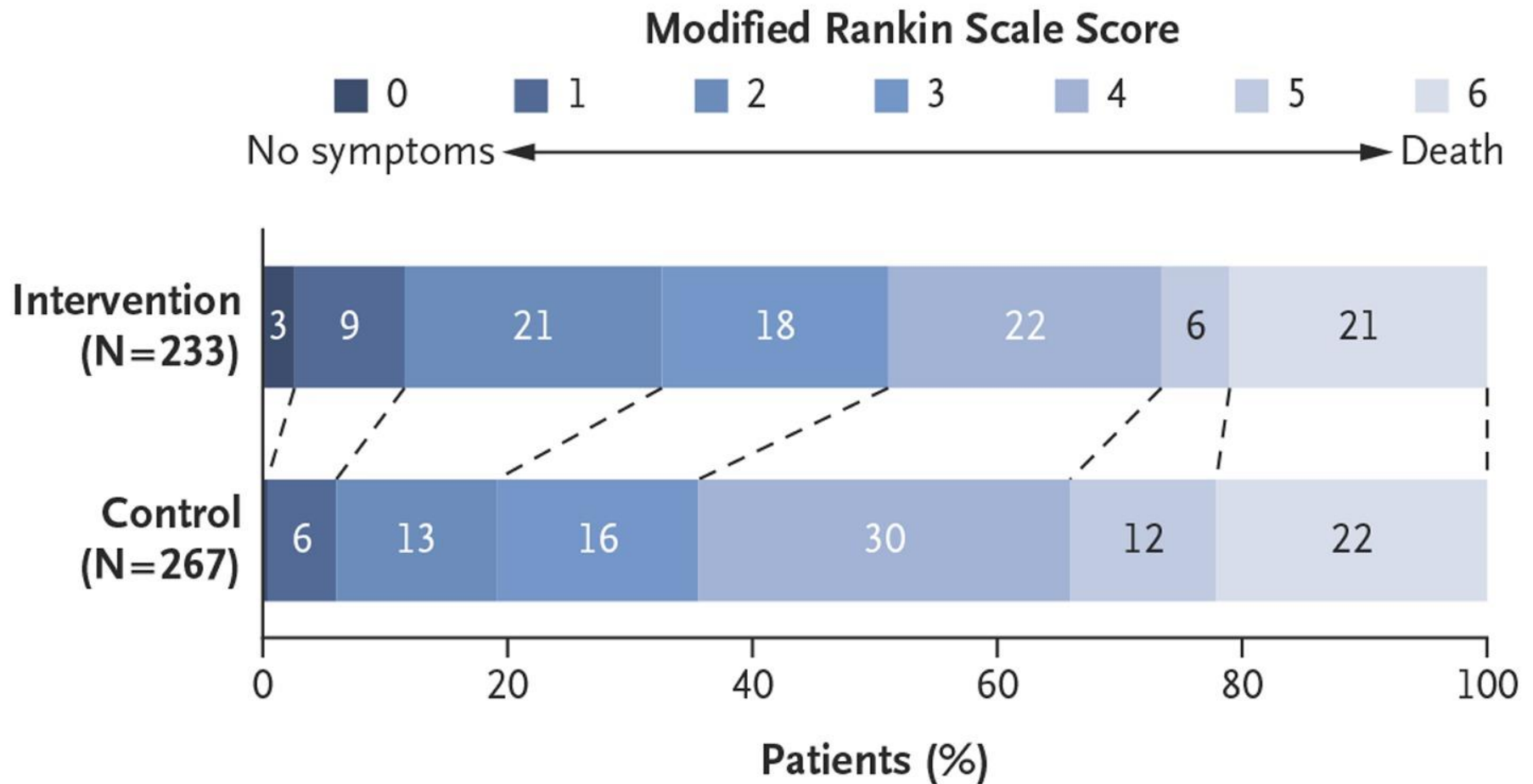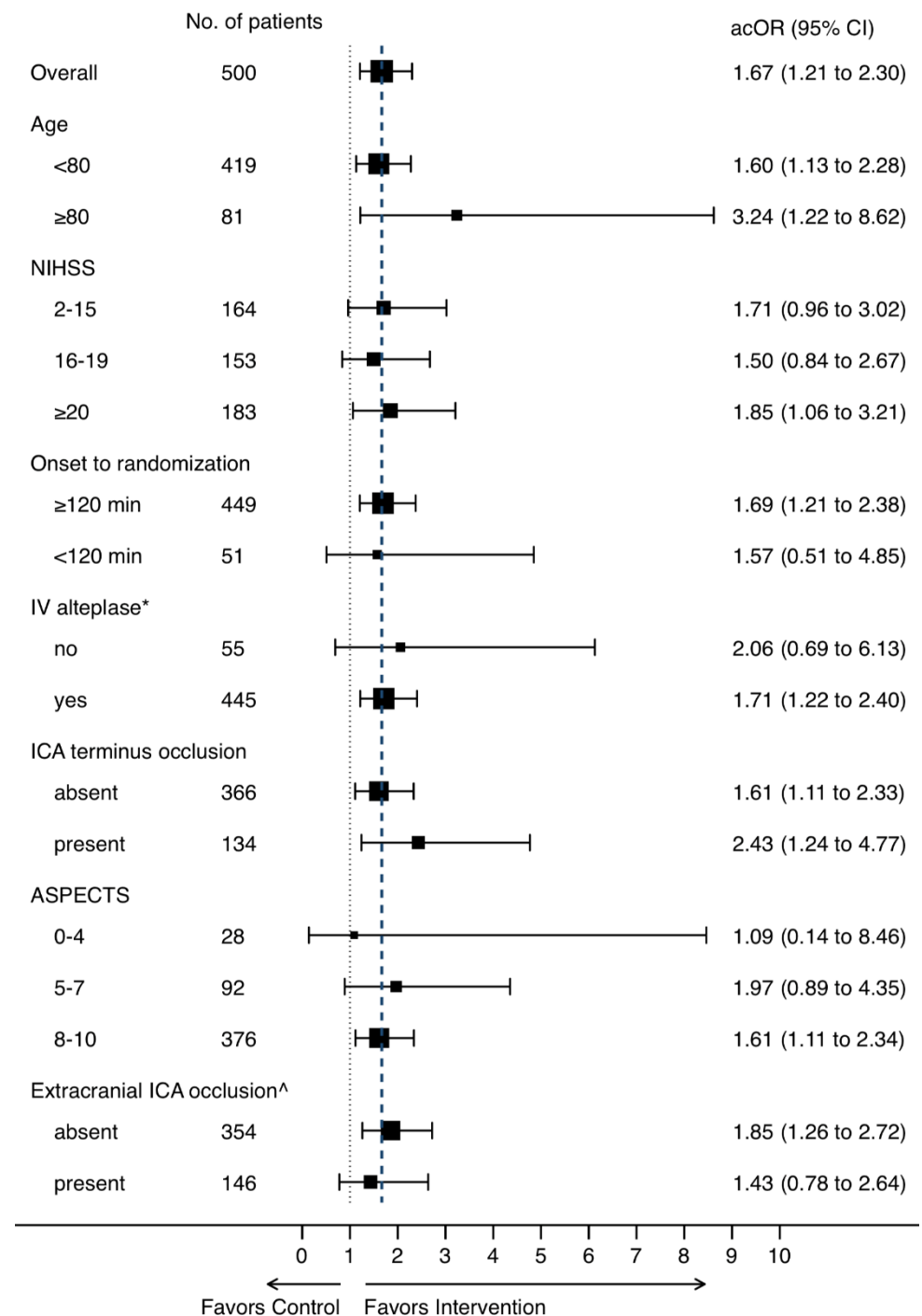- a score of 2 or higher

Berkhemer OA et al., 2015

MR CLEAN

- Patient Characteristics

Table 1. Baseline Characteristics of the 500 Patients.*

Characteristic	Intervention (N = 233)	Control (N = 267)
Age — yr		
Median	65.8	65.7
Interquartile range	54.5–76.0	55.5–76.4
Male sex — no. (%)	135 (57.9)	157 (58.8)
NIHSS score†		
Median (interquartile range)	17 (14–21)	18 (14–22)
Range	3–30	4–38
Location of stroke in left hemisphere — no. (%)	116 (49.8)	153 (57.3)
History of ischemic stroke — no. (%)	29 (12.4)	25 (9.4)
Atrial fibrillation — no. (%)	66 (28.3)	69 (25.8)
Diabetes mellitus — no. (%)	34 (14.6)	34 (12.7)
Prestroke modified Rankin scale score — no. (%)‡		
0	190 (81.5)	214 (80.1)
1	21 (9.0)	29 (10.9)
2	12 (5.2)	13 (4.9)
>2	10 (4.3)	11 (4.1)
Systolic blood pressure — mm Hg§	146±26.0	145±24.4
Treatment with IV alteplase — no. (%)	203 (87.1)	242 (90.6)
Time from stroke onset to start of IV alteplase — min		
Median	85	87
Interquartile range	67–110	65–116
ASPECTS — median (interquartile range)¶	9 (7–10)	9 (8–10)
Intracranial arterial occlusion — no./total no. (%)‖		
Intracranial ICA	1/233 (0.4)	3/266 (1.1)
ICA with involvement of the M1 middle cerebral artery segment	59/233 (25.3)	75/266 (28.2)
M1 middle cerebral artery segment	154/233 (66.1)	165/266 (62.0)
M2 middle cerebral artery segment	18/233 (7.7)	21/266 (7.9)
A1 or A2 anterior cerebral artery segment	1/233 (0.4)	2/266 (0.8)
Extracranial ICA occlusion — no./total no. (%)‖**	75/233 (32.2)	70/266 (26.3)
Time from stroke onset to randomization — min††		
Median	204	196
Interquartile range	152–251	149–266
Time from stroke onset to groin puncture — min		
Median	260	NA
Interquartile range	210–313	

Berkhemer OA et al., 2015

MR CLEAN: MRS SCORES AT 90 DAYS

Berkhemer OA et al., 2015

MR CLEAN
Subgroup Analyses

	No. of patients		acOR (95% CI)
Overall	500		1.67 (1.21 to 2.30)
Age			
<80	419		1.60 (1.13 to 2.28)
≥80	81		3.24 (1.22 to 8.62)
NIHSS			
2-15	164		1.71 (0.96 to 3.02)
16-19	153		1.50 (0.84 to 2.67)
≥20	183		1.85 (1.06 to 3.21)
Onset to randomization			
≥120 min	449		1.69 (1.21 to 2.38)
<120 min	51		1.57 (0.51 to 4.85)
IV alteplase*			
no	55		2.06 (0.69 to 6.13)
yes	445		1.71 (1.22 to 2.40)
ICA terminus occlusion			
absent	366		1.61 (1.11 to 2.33)
present	134		2.43 (1.24 to 4.77)
ASPECTS			
0-4	28		1.09 (0.14 to 8.46)
5-7	92		1.97 (0.89 to 4.35)
8-10	376		1.61 (1.11 to 2.34)
Extracranial ICA occlusion^			
absent	354		1.85 (1.26 to 2.72)
present	146		1.43 (0.78 to 2.64)

Favors Control ← → Favors Intervention

Berkhemer OA et al., 2015

APECTS: ALBERTA STROKE PROGRAM EARLY CT SCORE

Hill, 2003

ET Trials: ASPECTS

Study or Subgroup	log[Odds Ratio]	SE	Patient Total	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
1.1.1 ASPECTS 8-10						
ESCAPE	1.01160091	0.26469071	250	19.5%	2.75 [1.64, 4.62]	
MR CLEAN	0.476234	0.190774	376	37.6%	1.61 [1.11, 2.34]	
REVASCAT	0.89199804	0.40907195	105	8.2%	2.44 [1.09, 5.44]	
SWIFT PRIME	1.04380405	0.34731973	142	11.4%	2.84 [1.44, 5.61]	
Subtotal (95% CI)			873	76.7%	2.10 [1.61, 2.73]	
Heterogeneity: Chi² = 3.87, df = 3 (P = 0.28); I² = 22%						
Test for overall effect: Z = 5.55 (P < 0.00001)						
1.1.2 ASPECTS 5-7						
ESCAPE	1.036737	0.626605	54	3.5%	2.82 [0.83, 9.63]	
MR CLEAN	0.67803354	0.40415424	92	8.4%	1.97 [0.89, 4.35]	
REVASCAT	0.48858002	0.43184748	101	7.3%	1.63 [0.70, 3.80]	
SWIFT PRIME	0.985817	0.698169	43	2.8%	2.68 [0.68, 10.53]	
Subtotal (95% CI)			290	22.0%	2.04 [1.25, 3.32]	
Heterogeneity: Chi² = 0.70, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 2.85 (P = 0.004)						
1.1.3 ASPECTS 0-4						
MR CLEAN	0.086178	1.045496	28	1.3%	1.09 [0.14, 8.46]	
Subtotal (95% CI)			28	1.3%	1.09 [0.14, 8.46]	
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)			1191	100.0%	2.07 [1.64, 2.60]	
Heterogeneity: Chi² = 4.96, df = 8 (P = 0.76); I² = 0%						
Test for overall effect: Z = 6.20 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.39, df = 2 (P = 0.82), I² = 0%						

0.1 0.2 0.5 1 2 5 10
Favours [control]   Favours [thrombectomy]

Balami, 2015

STENT RETRIEVER TRIALS

Study	Total Study Population	Endovascular Treatment	Modified Rankin Score of 0-2 at 3 mo in Endovascular Group, % of Patients	Absolute Increase in Improved vs Control Groups, % of Patients
MR CLEAN	500	233	33	14
ESCAPE	315	165	53	24
REVASCAT	206	103	44	16
SWIFT PRIME	196	98	60	25
EXTEND-IA	70	35	72	33

Alberts, 2015

META-ANALYSIS OF FIRST 5 STENT RETRIEVER TRIALS

Saver, 2016
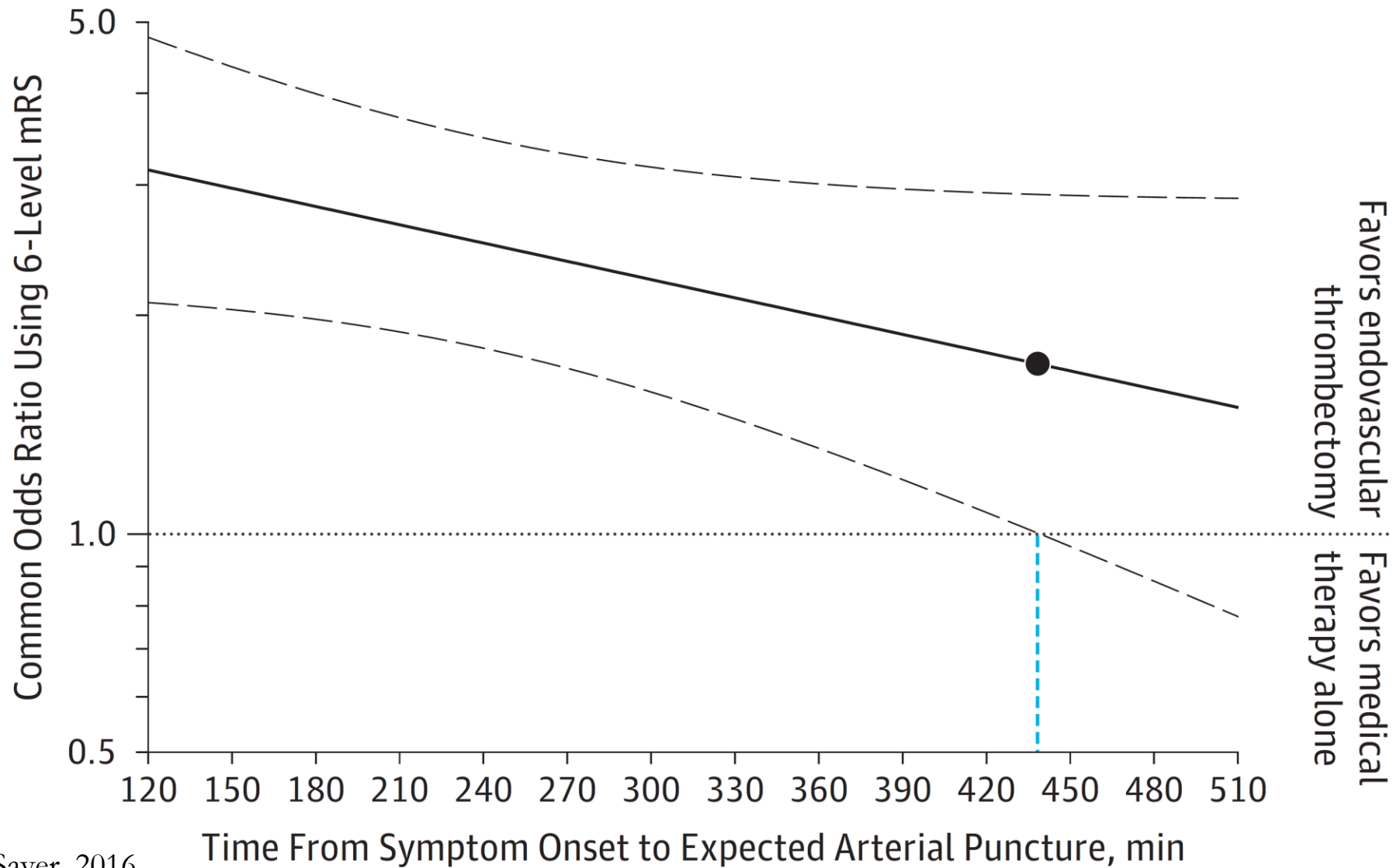
2015 AHA/ASA Class I: Level A Guidelines for ET

- Patients eligible for intravenous r-tPA should receive intravenous r-tPA

- Patients should receive ET with a stent retriever if they meet all the following criteria

  - prestroke mRS score 0 to 1

  - acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset

  - causative occlusion of the IC ICA or M1

  - age ≥18 years,

  - NIHSS score of ≥6,

  - ASPECTS of ≥6, and

  - treatment can be initiated (groin puncture) within 6 hours of symptom onset

- Emergency imaging of the brain is recommended before initiating any specific treatment for acute stroke. In most instances, nonenhanced CT will provide the necessary information

- If ET is contemplated, a noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient but should not delay iv r-tPA if indicated
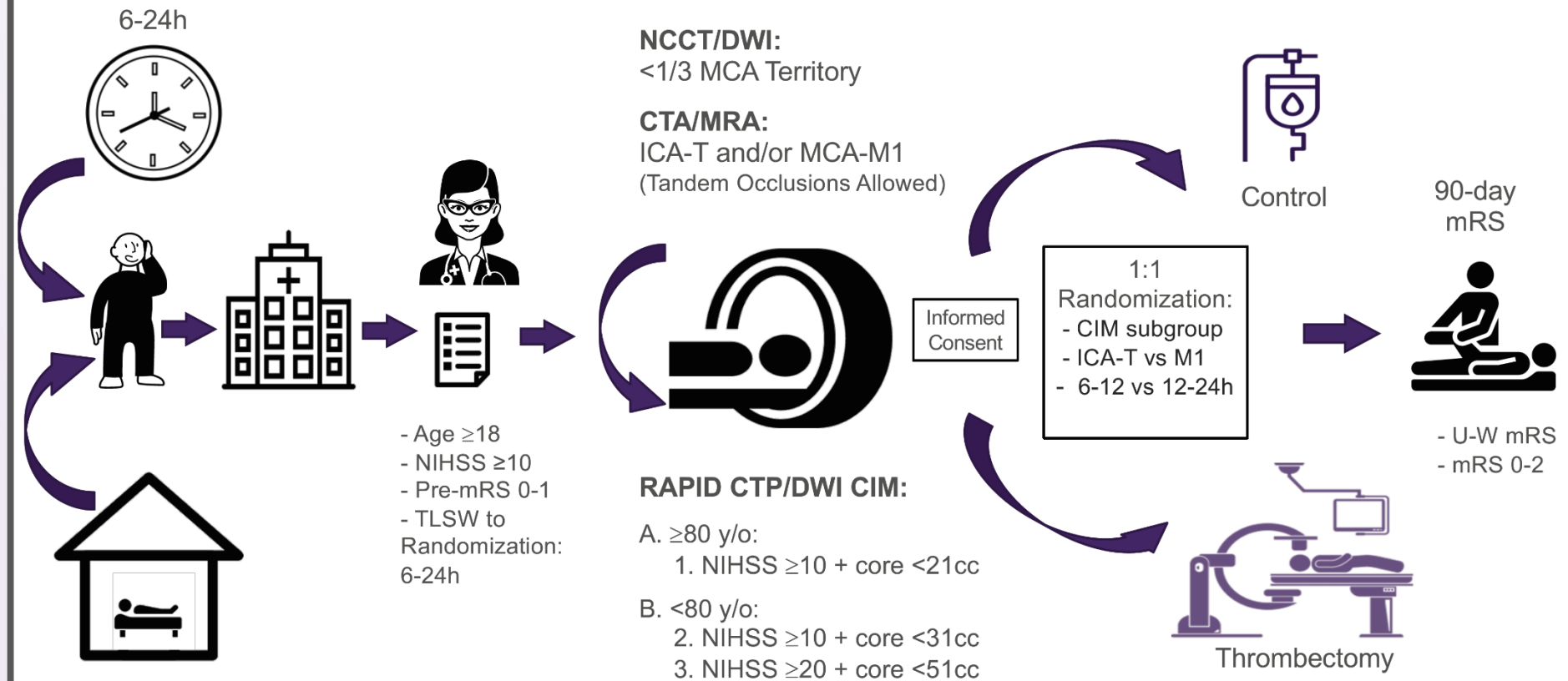
Powers, 2015

2015 AHA/ASA Guidelines for ET based on Class I: Level A data

○ Patients should be transported rapidly to the closest available certified primary stroke center or comprehensive stroke center or, if no such centers exist, the most appropriate institution that provides emergency stroke care as described in the 2013 guidelines. In some instances, this may involve air medical transport and hospital bypass.

○ Regional systems of stroke care should be developed. These should consist of:

- Healthcare facilities that provide initial emergency care including administration of intravenous r-tPA, including primary stroke centers, comprehensive stroke centers, and other facilities.

- Centers capable of performing endovascular stroke treatment with comprehensive periprocedural care, including comprehensive stroke centers and other healthcare facilities, to which rapid transport can be arranged when appropriate

Powers, 2015

DAWN METHODS

Study Methods: Workflow

6-24h

NCCT/DWI:
<1/3 MCA Territory

CTA/MRA:
ICA-T and/or MCA-M1
(Tandem Occlusions Allowed)

Informed Consent

Control

90-day mRS

1:1 Randomization:
- CIM subgroup
- ICA-T vs M1
- 6-12 vs 12-24h

- U-W mRS
- mRS 0-2

- Age ≥18
- NIHSS ≥10
- Pre-mRS 0-1
- TLSW to Randomization: 6-24h

RAPID CTP/DWI CIM:

A. ≥80 y/o:
   1. NIHSS ≥10 + core <21cc

B. <80 y/o:
   2. NIHSS ≥10 + core <31cc
   3. NIHSS ≥20 + core <51cc

Thrombectomy

Nogueira et al, 2017

DAWN
Baseline
Characteristics

Nogueira et al, 2017

Table 1. Characteristics of the Patients at Baseline.*

Variable	Thrombectomy Group (N=107)	Control Group (N=99)
Age — yr	69.4±14.1	70.7±13.2
Age ≥80 yr — no. (%)	25 (23)	29 (29)
Male sex — no. (%)	42 (39)	51 (52)
Atrial fibrillation — no. (%)	43 (40)	24 (24)
Diabetes mellitus — no. (%)	26 (24)	31 (31)
Hypertension — no. (%)	83 (78)	75 (76)
Previous ischemic stroke or transient ischemic attack — no. (%)	12 (11)	11 (11)
NIHSS score†		
Median	17	17
Interquartile range	13–21	14–21
10 to 20 — no. (%)	78 (73)	72 (73)
Treatment with intravenous alteplase — no. (%)	5 (5)	13 (13)
Infarct volume — ml		
Median	7.6	8.9
Interquartile range	2.0–18.0	3.0–18.1
Type of stroke onset — no. (%)‡		
On awakening	67 (63)	47 (47)
Unwitnessed stroke	29 (27)	38 (38)
Witnessed stroke	11 (10)	14 (14)
Occlusion site — no. (%)§		
Intracranial internal carotid artery	22 (21)	19 (19)
First segment of middle cerebral artery	83 (78)	77 (78)
Second segment of middle cerebral artery	2 (2)	3 (3)
Interval between time that patient was last known to be well and randomization — hr		
Median	12.2	13.3
Interquartile range	10.2–16.3	9.4–15.8
Range	6.1–23.5	6.5–23.9
Time from first observation of symptoms to randomization — hr		
Median	4.8	5.6
Interquartile range	3.6–6.2	3.6–7.8

DAWN
RESULTS

- NNT for mRS ≤ 2
  - 2.8
- Symptomatic hemorrhage
  - 6%(MT) vs. 3%

Nogueira et al, 2017
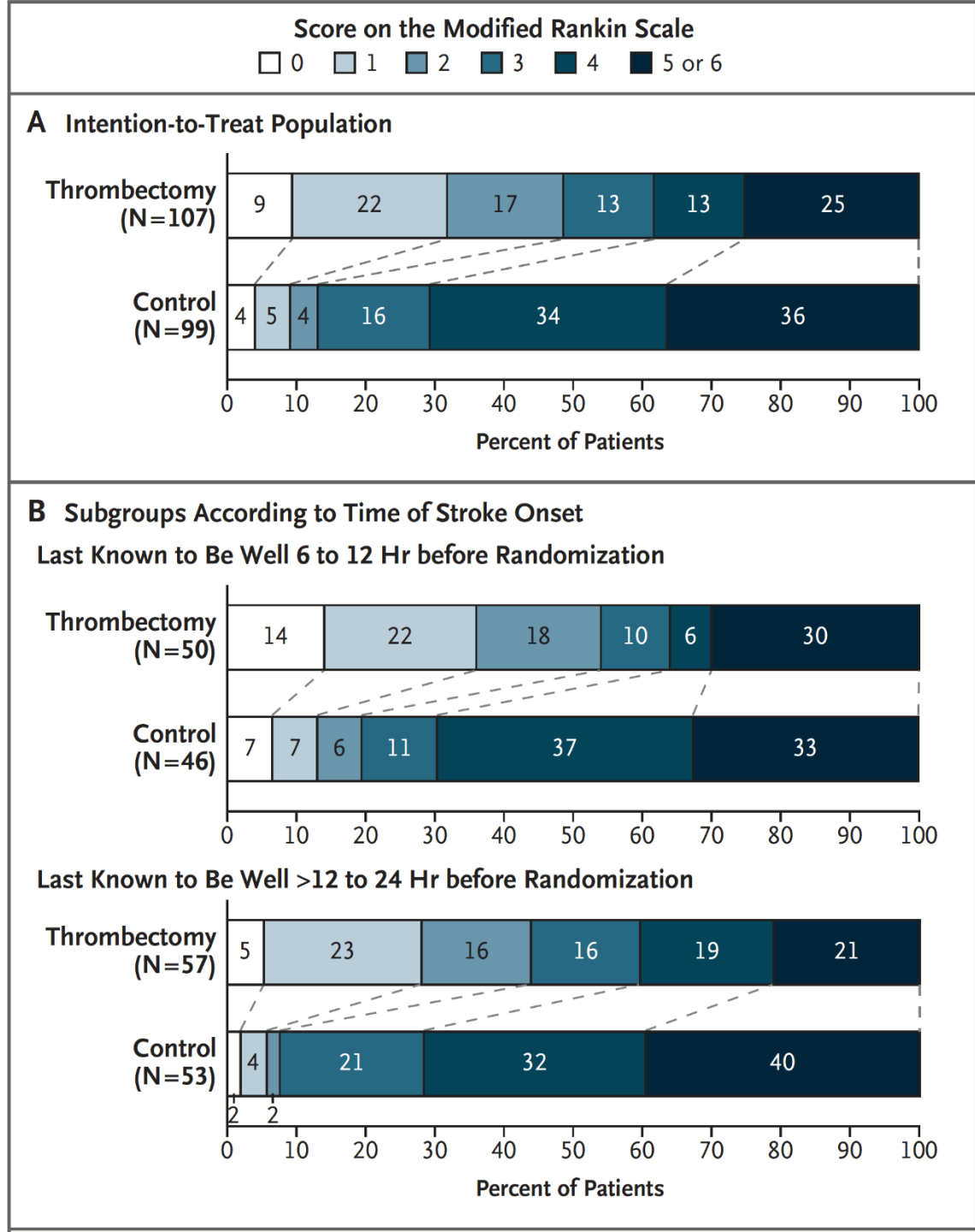
DEFUSE 3: CLINICAL INCLUSION CRITERIA

- Signs and symptoms consistent with acute anterior circulation stroke

- Age 18-90 years

- Baseline NIHSSS ≥ 6 immediately prior to randomization

- Endovascular treatment between 6-16 hours of stroke LKW

- Pre-stroke mRS score 0-2

DEFUSE 3: Neuroimaging Inclusion Criteria

1) MRA / CTA demonstrates

- M1 segment MCA occlusion, or

- ICA occlusion (cervical or intracranial; with or without tandem MCA lesions)

AND
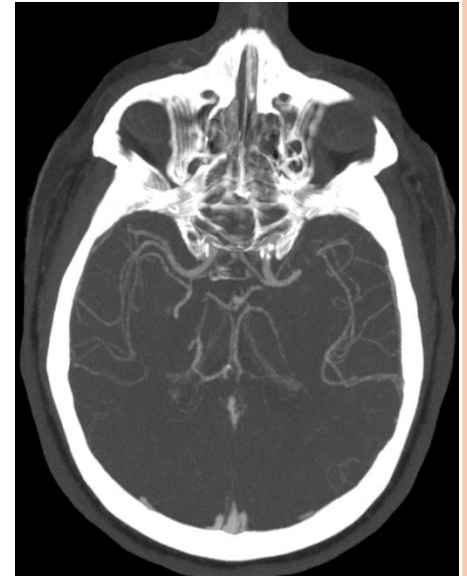
2) Target Mismatch Profile on CT perfusion or MRI (RAPID)

- Ischemic core < 70 mL

- Mismatch ratio $\geq$ 1.8

- Mismatch ≥ 15 mL

CBF (0.3 threshold) 6 ml   Hypoperfusion (Tmax>6s) 82 ml

Mismatch Volume: 76 ml
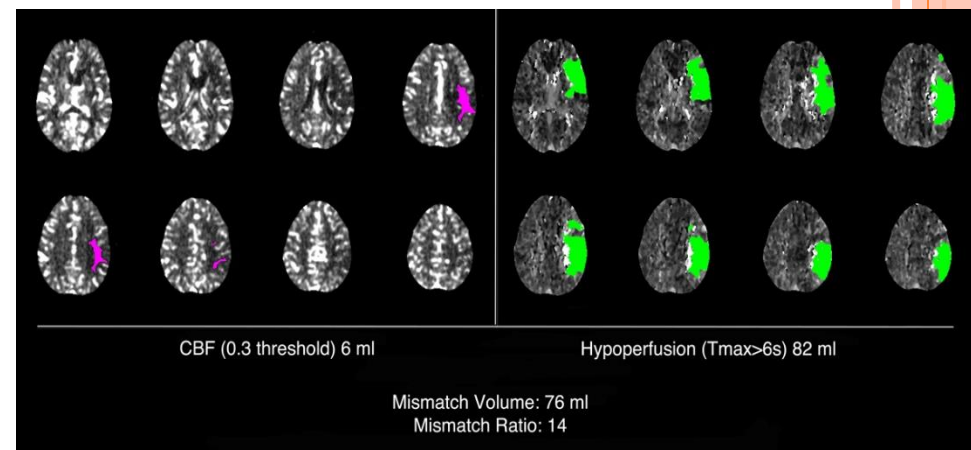Mismatch Ratio: 14

Albers, 2018

DEFUSE 3

Table 1. Baseline Characteristics of the Patients and Features of Thrombectomy.*

Characteristic	Endovascular Therapy (N=92)	Medical Therapy (N=90)
Median age (IQR) — yr	70 (59–79)	71 (59–80)
Female sex — no. (%)	46 (50)	46 (51)
Median NIHSS score (IQR)†	16 (10–20)	16 (12–21)
Stroke onset witnessed — no. (%)		
Yes‡	31 (34)	35 (39)
No		
Symptoms were present on awakening	49 (53)	42 (47)
Symptoms began during wakefulness	12 (13)	13 (14)
Treatment with intravenous t-PA — no. (%)§	10 (11)	8 (9)
Imaging characteristics¶		
Qualifying imaging — no. (%)		
CT perfusion imaging	69 (75)	64 (71)
Diffusion and perfusion MRI	23 (25)	26 (29)
Median volume of ischemic core (IQR) — ml	9.4 (2.3–25.6)	10.1 (2.1–24.3)
Median volume of perfusion lesion (IQR) — ml‖	114.7 (79.3–146.3)	116.1 (73.4–158.2)
Occlusion site on baseline CTA or MRA — no. (%)		
Internal carotid artery	32 (35)	36 (40)
Middle cerebral artery**	60 (65)	54 (60)
Median ASPECTS on baseline CT (IQR)††	8 (7–9)	8 (7–9)
Process measures — hr:min		
Median time from stroke onset to qualifying imaging (IQR)	10:29 (8:09–11:40)	9:55 (7:59–12:20)
Median time from stroke onset to randomization (IQR)	10:53 (8:46–12:21)	10:44 (8:42–13:04)
Median time from qualifying imaging to femoral puncture (IQR)	0:59 (0:39–1:27)	NA
Median time from femoral puncture to reperfusion (IQR)	0:38 (0:26–0:59)	NA

Albers, 2018

DEFUSE 3 Results

- NNT for mRS ≤ 2
  - 3.6
- Symptomatic hemorrhage
  - 7%(MT) vs. 4%

Albers, 2018
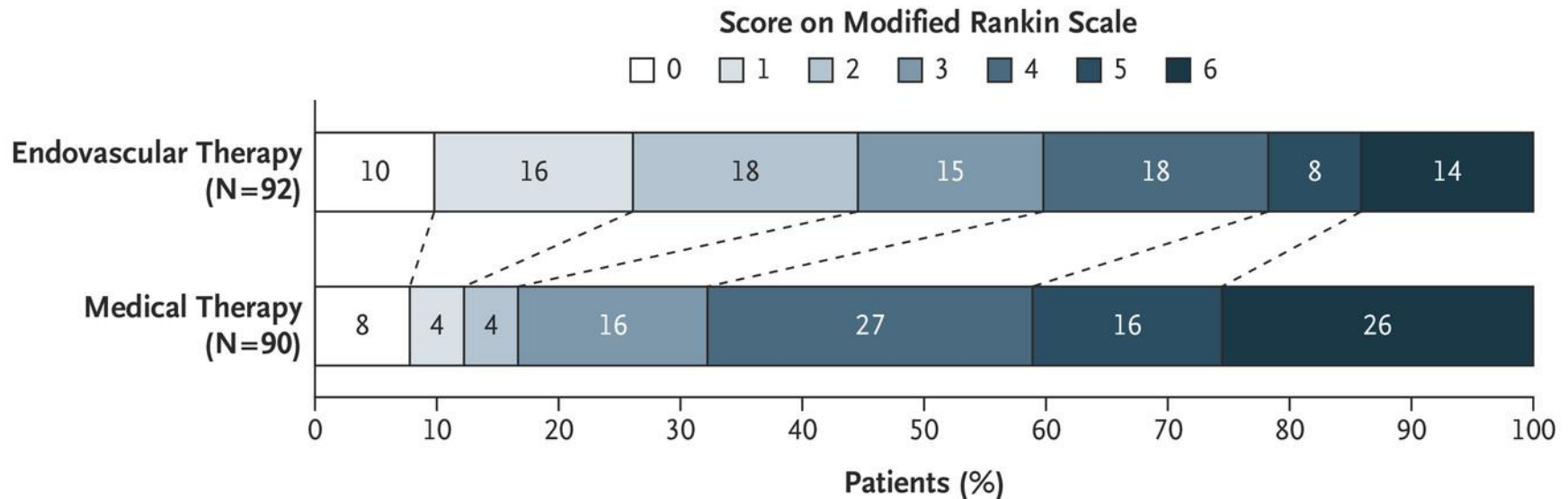
Stent Retriever Trials

Study	Total N	Window From LKW (hours)	% Rx tPA	Brain Imaging Selection	% mRS ≤ 2 MT group	Increase in % mRS ≤ 2	NNT for mRS ≤ 2
MR CLEAN	500	< 6	89	CT no bleed	33	14	7.1
ESCAPE	315	< 12	76	ASPECTS 6-10 Mod-good collaterals	53	24	4.2
REVASCAT	206	< 6	73	ASPECTS 7-10 CT APECTS 6-10 MRI	44	16	6.3
SWIFT PRIME	196	< 6	100	Penumbral imaging Small-mod core	60	25	4.0
EXTEND-IA	70	< 6	100	CTP mismatch	72	33	3.0
DAWN	206	6-24	9	DWI or CTP core	49	36	2.8
DEFUSE 3	182	6-16	10	Penumbral imaging	45	28	3.6

2018 Guidelines Update on Late Window ET

- In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended. (I, A)
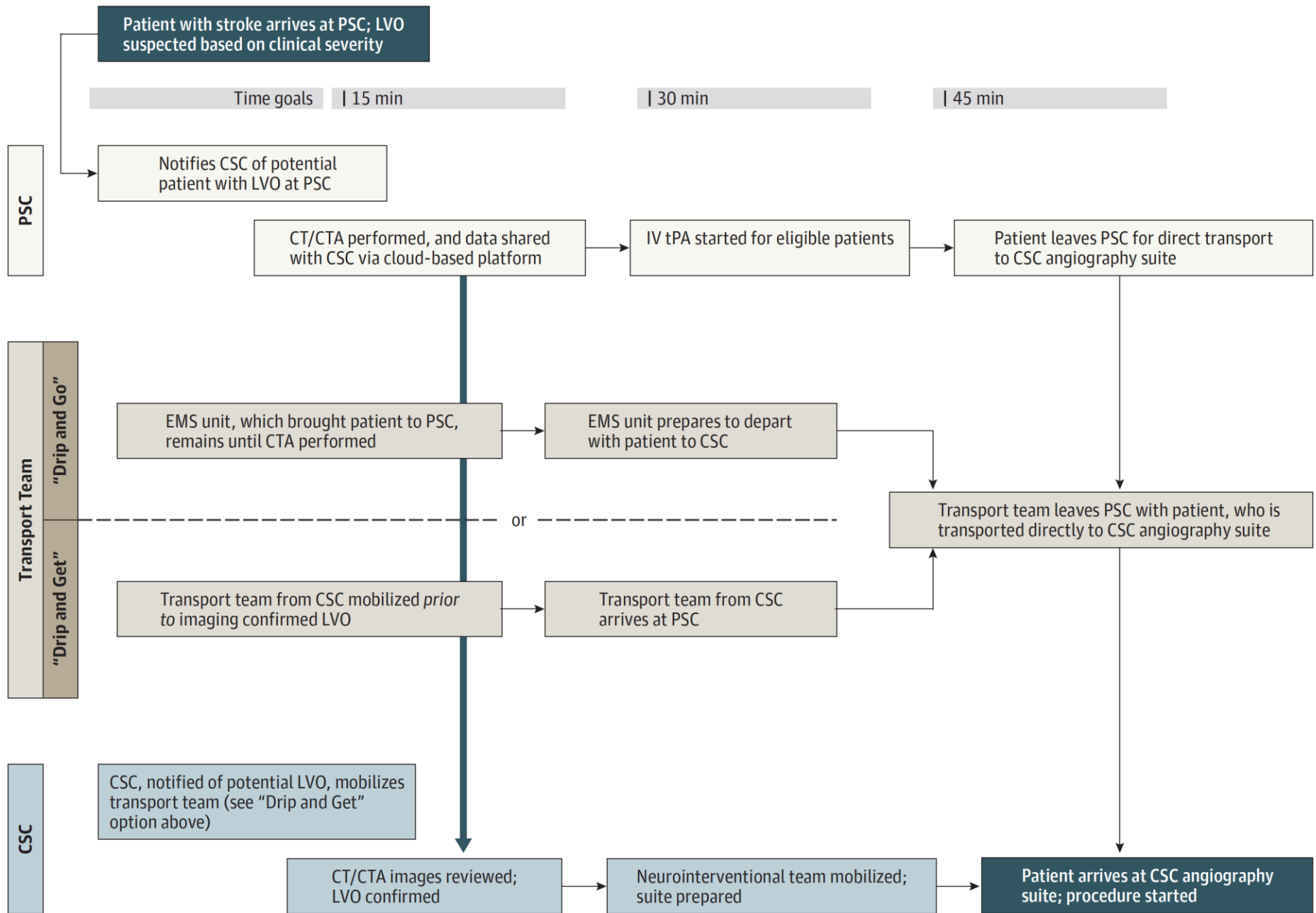
- In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable. (IIa, B-R)

Primary Stroke Center Protocol for Suspected LVO

- Small, retrospective cohort study 7/1/15 to 5/31/16
- 14 regional PSCs 4 to 47 miles from a CSC
- Protocol
  - Notify the CSC on arrival at PSC if LVO suspected (LAMS ≥ 4)
  - Early mobilization of transport team
  - Perform CTA concurrently with NCCT at PSC
  - Share imaging data with the CSC using a cloud-based platform
  - Direct transport to the CSC angiography suite
- Protocol adherence
  - Partial, 48 patients (69%)
  - Full, 22 patients (31%)

McTaggart, 2017

PSC

Patient with stroke arrives at PSC; LVO suspected based on clinical severity

Time goals | 15 min | 30 min | 45 min

Notifies CSC of potential patient with LVO at PSC

CT/CTA performed, and data shared with CSC via cloud-based platform

IV tPA started for eligible patients

Patient leaves PSC for direct transport to CSC angiography suite

Transport Team

"Drip and Go"

EMS unit, which brought patient to PSC, remains until CTA performed

EMS unit prepares to depart with patient to CSC

or

"Drip and Get"

Transport team from CSC mobilized *prior to* imaging confirmed LVO

Transport team from CSC arrives at PSC

Transport team leaves PSC with patient, who is transported directly to CSC angiography suite

CSC

CSC, notified of potential LVO, mobilizes transport team (see "Drip and Get" option above)

CT/CTA images reviewed; LVO confirmed

Neurointerventional team mobilized; suite prepared

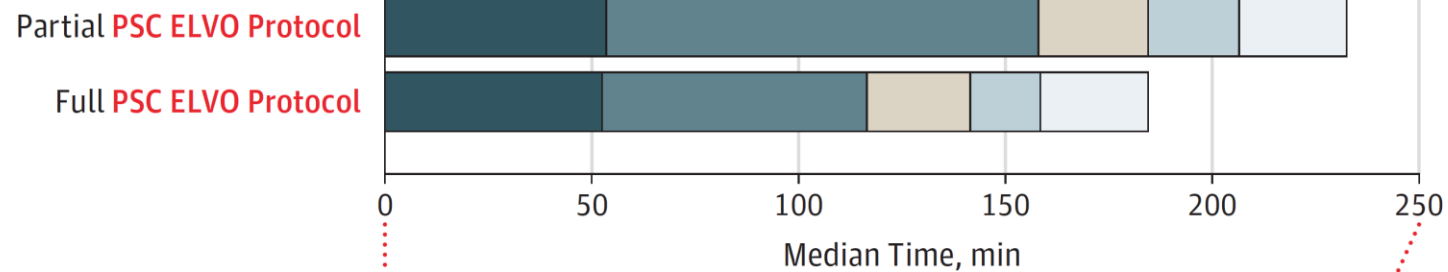Patient arrives at CSC angiography suite; procedure started

McTaggart, 2017

DIFFERENCES IN WORKFLOW TIMES BETWEEN PARTIALLY AND FULLY EXECUTED PROTOCOL

Metric	Partial Protocol		Full Protocol		P Value
	Median (IQR)	95% CI	Median (IQR)	95% CI	
PSC					
OTD	53.5 (37-118)	45.0-67.0	52.5 (32-129)	32.0-79.0	.64
DTN	65.0 (55-96)	58.0-78.0	39.5 (32-51)	30.0-51.0	<.001
Onset to IV tPA	113.0 (92-165)	100.0-125.0	92.0 (60-112)	60.0-112.0	.01
CSC					
OTPunc	218.5 (176-326)	191.0-255.0	185.0 (137-209)	137.0-205.0	.02
OTRep	262.0 (203-372)	223.0-316.0	222.0 (165-275)	165.0-263.0	.04
PSC NCCT to CSCPunc	133.0 (108-165)	120.0-139.0	97.5 (76-120)	76.0-110.0	<.001
PSC CTA to CSCPunc	110.5 (79-136)	95.0-122.0	93.0 (69-122)	69.0-111.0	.16
DIDO PSC	104.5 (78-121)	82.0-112.0	64.0 (51-88)	51.0-71.0	<.001
PSCDoor to CSCPunc	151.0 (132-187)	141.0-166.0	111.0 (88-137)	88.0-130.0	<.001
PSCDoor to CSCRep	179.0 (159-237)	164.0-210.0	132.0 (113-183)	113.0-172.0	<.001
CSCDoor to CSCPunc	22.0 (17-32)	19.0-26.0	17.0 (14-20)	14.0-20.0	.005
CSC reperfusion time	26.0 (15-41)	19.0-32.0	26.0 (15-30)	15.0-30.0	.82

A PSC ELVO protocol

Legend: Onset to PSCDoor | PSC DIDO | Transport time | CSCDoor to CSCPunc | CSCPunc to CSCRecan

Partial PSC ELVO Protocol
Full PSC ELVO Protocol

Median Time, min (0, 50, 100, 150, 200, 250)

B Onset to recanalization (PSC ELVO protocol vs other studies)

IMS3[11] Transfer
Sun et al[13] Transfer
SWIFT PRIME[12] Transfer
HERMES[7] Transfer
Partial PSC ELVO Protocol
Full PSC ELVO Protocol
ESCAPE[14]
SWIFT PRIME[12] Direct
HERMES[7] Direct

Median Time, min (0, 50, 100, 150, 200, 250, 300, 350, 400)

McTaggart, 2017