Direct to Thrombectomy in the Management of Acute Ischemic Strokes with Large Vessel Occlusions

Jeffrey L. Saver, MD,
Director, UCLA Comprehensive Stroke and Vascular Neurology Program
SA Vice-Chair and Professor of Neurology, DGSOM

JLS Disclosures

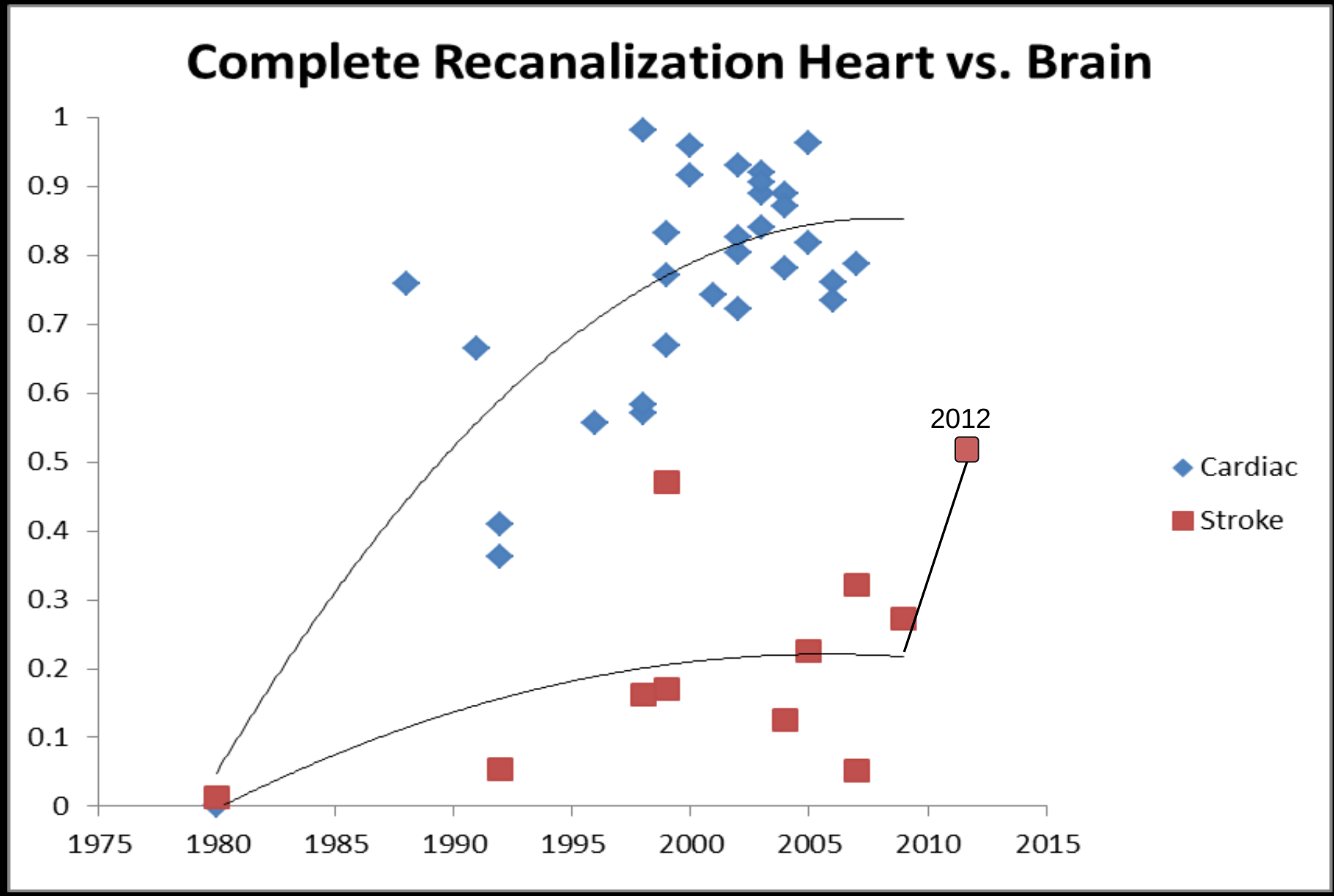
- Employee of the University of California. The University of California has patent rights in retrieval devices for stroke.
- Unpaid site investigator in multicenter trials run by Medtronic, Stryker, Cerenovus for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled.
- Receives compensation for services as a scientific consultant regarding rigorous trial design and conduct to Medtronic, Stryker, Cerenovus, Rapid Medical, Diffusion Pharma, BrainsGate, and Boehringer Ingelheim (prevention only).

Features of Pivotal Embolectomy Trials

Trial	Size	Intervention	Time	CTA/ MRA	Imaging	TPA in All Lytic-Eligible Pts	TPA Ineligible Pts Also Enrolled	Results
MR CLEAN	500	Variable (97% SR)	6 hr	+	<1/3 MCA	✓	Yes	Positive
ESCAPE	31	Variable (86% SR)	12 hr	+	Collat < 50%	✓	Yes	Positive
EXTEND IA	70	Solitaire	6 hr	+	RAPID Mismatch	✓	No	Positive
SWIFT PRIME	196	Solitaire	6 hr	+	A ≥ 6 RAPID	✓	No	Positive
REVASCAT	206	Solitaire	8 hr	+	A ≥ 6/7	✓	Yes	Positive
THRACE	414	Variable (Primarily SR)	R 4h	HVS ≥ 8mm		✓	No	Positive
THERAPY	108	Penumbra 3D		+	< 1/3 MCA	✓	No	Trend Positive

Bridging Therapy Patients Dominate in Completed RCTs

Trial	TPA Patients	TPA-Ineligible Patients
MR CLEAN	445	55
ESCAPE	238	77
EXTEND IA	70	0
SWIFT PRIME	196	0
REVASCAT	150	56
Total	1099	188
Percent	**85.4%**	**14.6%**



--Patel + Saver, Stroke 2013

--Saver et al, Lancet 2012; Nogueira et al, Lancet 2012

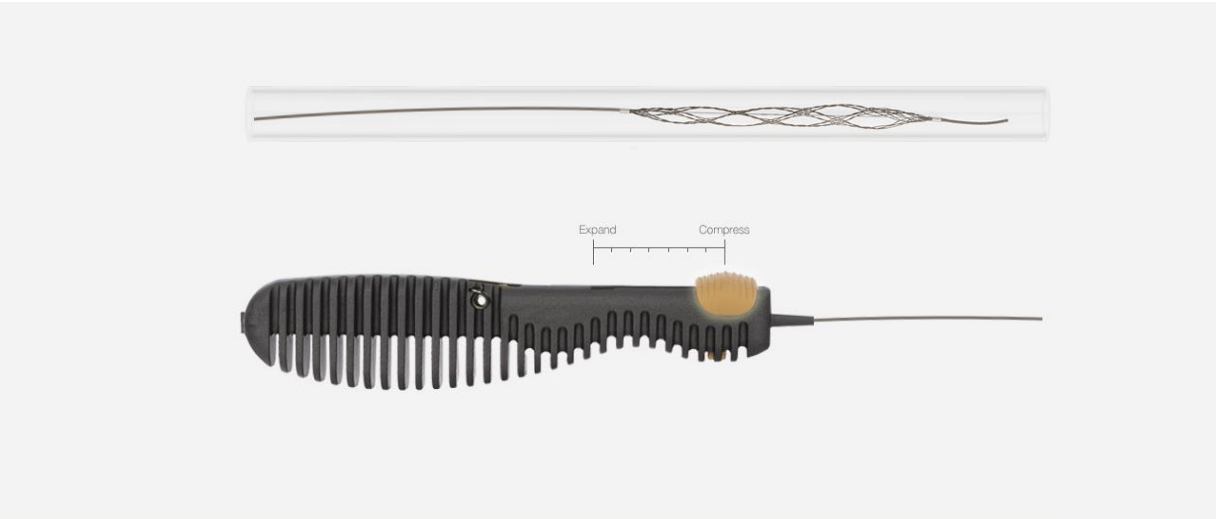
--Gupta, Saver et al, Stroke 2021

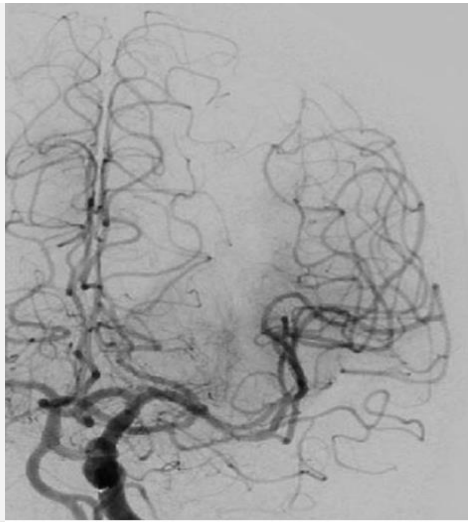
Improved Reperfusion Rates via Device Proliferation and Innovation

- Retrievers
  - » Solitaire (Medtronic)
  - » Trevo (Stryker)
  - » Catch (Balt)
  - » Preset (Phenox)
  - » EmboTrap (Neuravia)
  - » Separator 3D (Penumbra)
  - » Revive (Codman)
  - » Mindframe (Medtronic)
  - » Golden (Amnis)
  - » Tigertriever (Rapid Medical)
- Aspiration catheters
  - » Max ACE (Penumbra)
  - » Arc (Medtronic)
  - » SOFIA (Microvention)
  - » Cat-6 (Stryker)

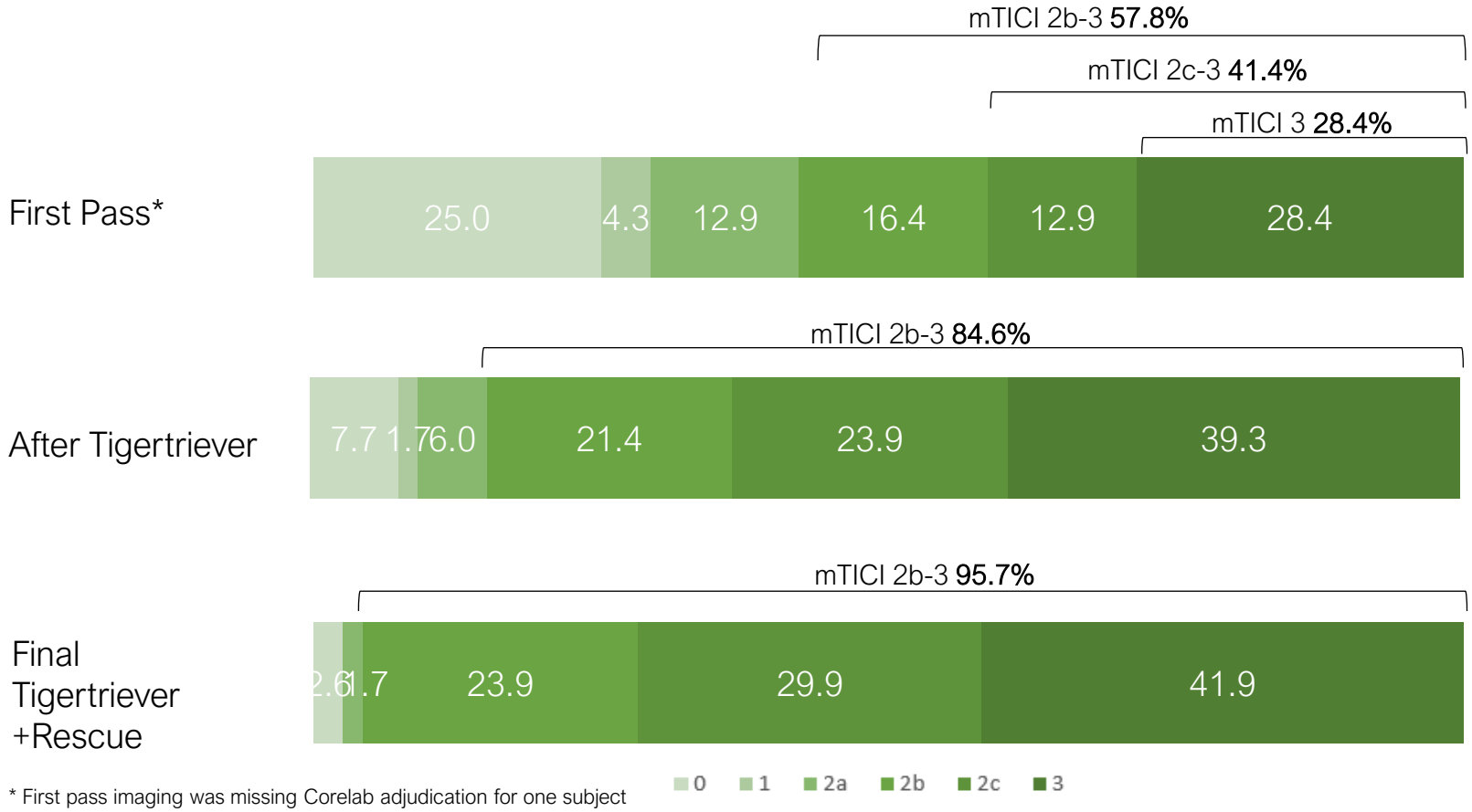
New class of radially-adjustable stentrievers for acute ischemic stroke

Tigertriever





Revascularization Outcomes (N=117, Core lab Adjudicated)



* First pass imaging was missing Corelab adjudication for one subject

--Gupta, Saver et al, Stroke 2021

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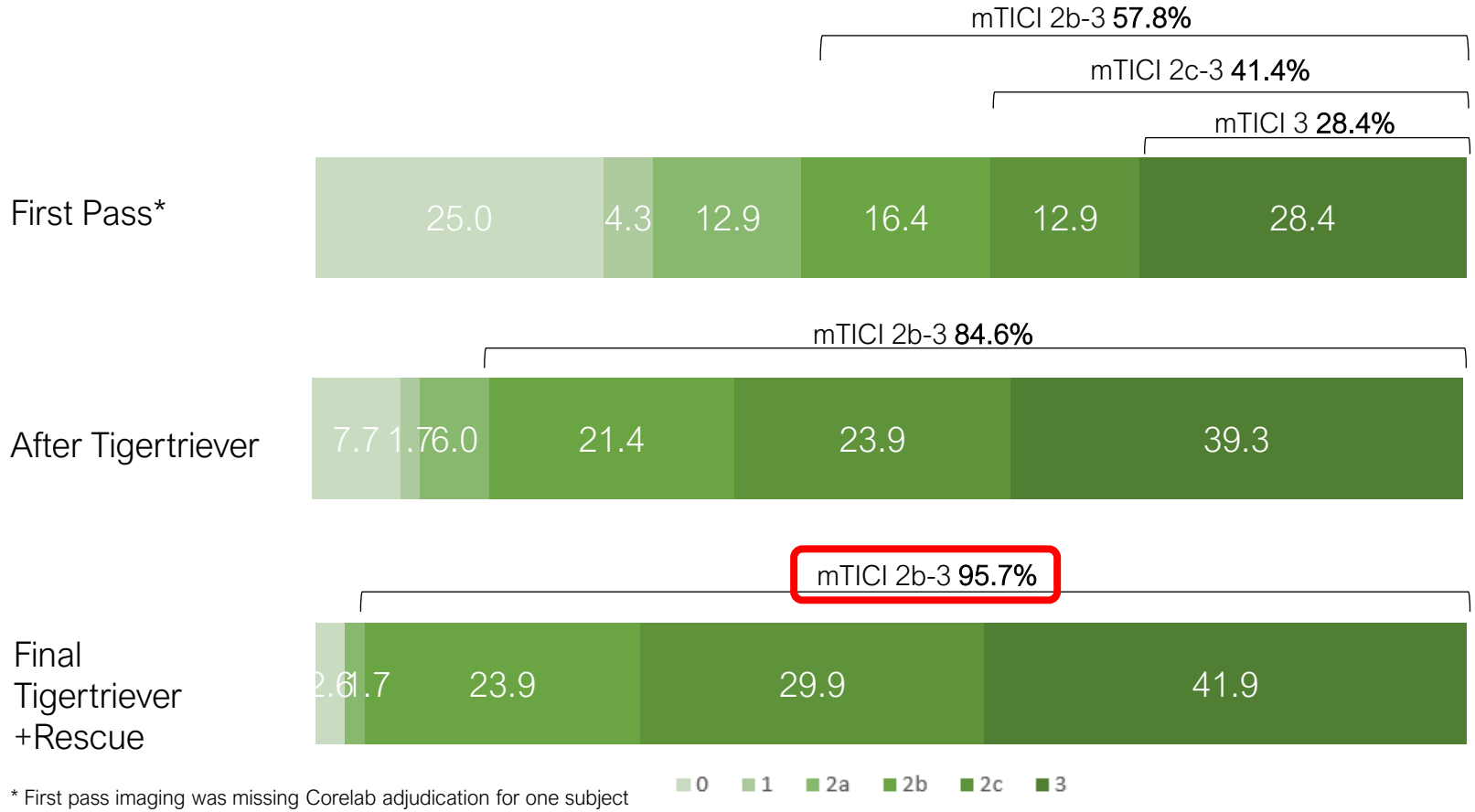

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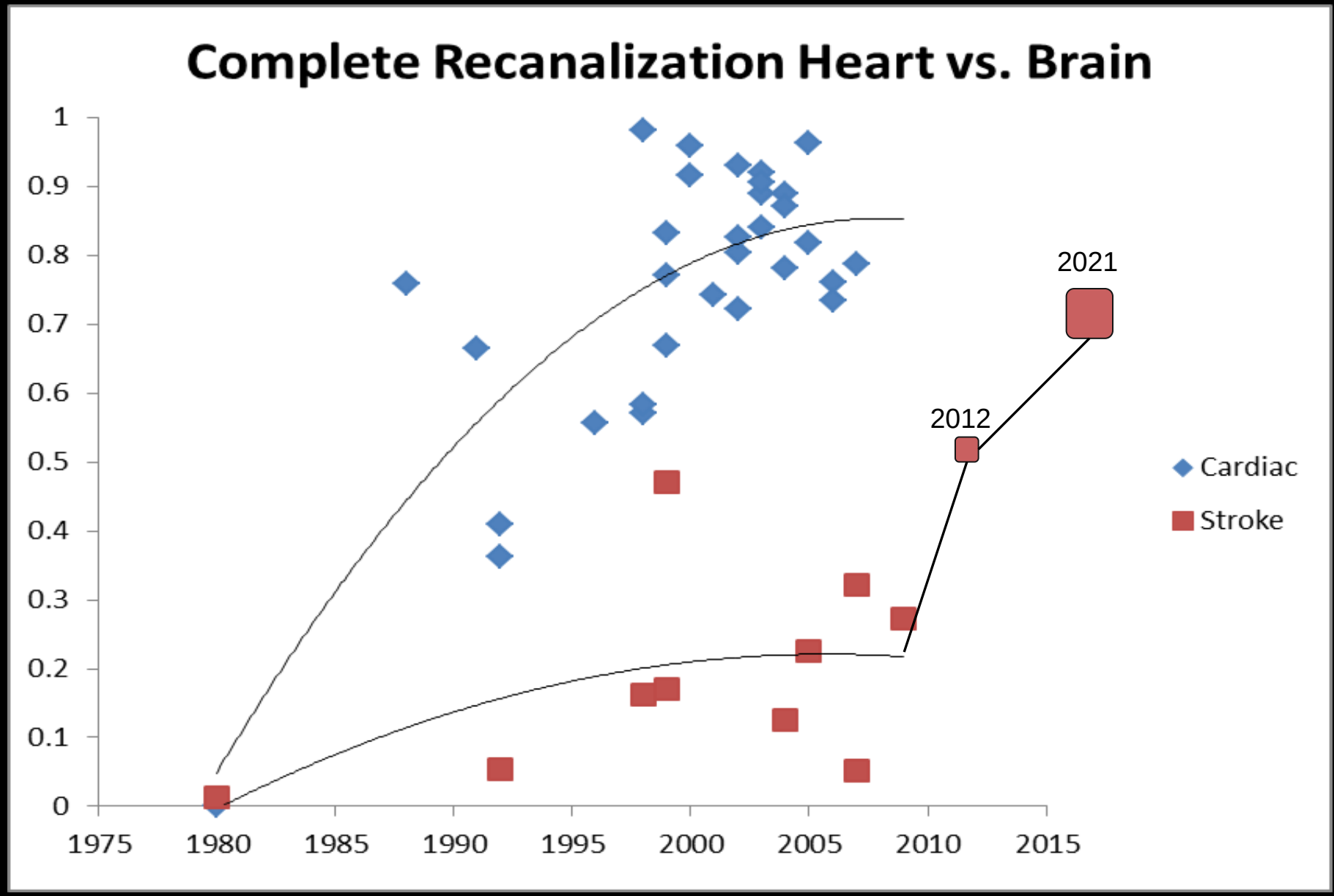

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--Saver et al, Lancet 2012; Nogueira et al, Lancet 2012

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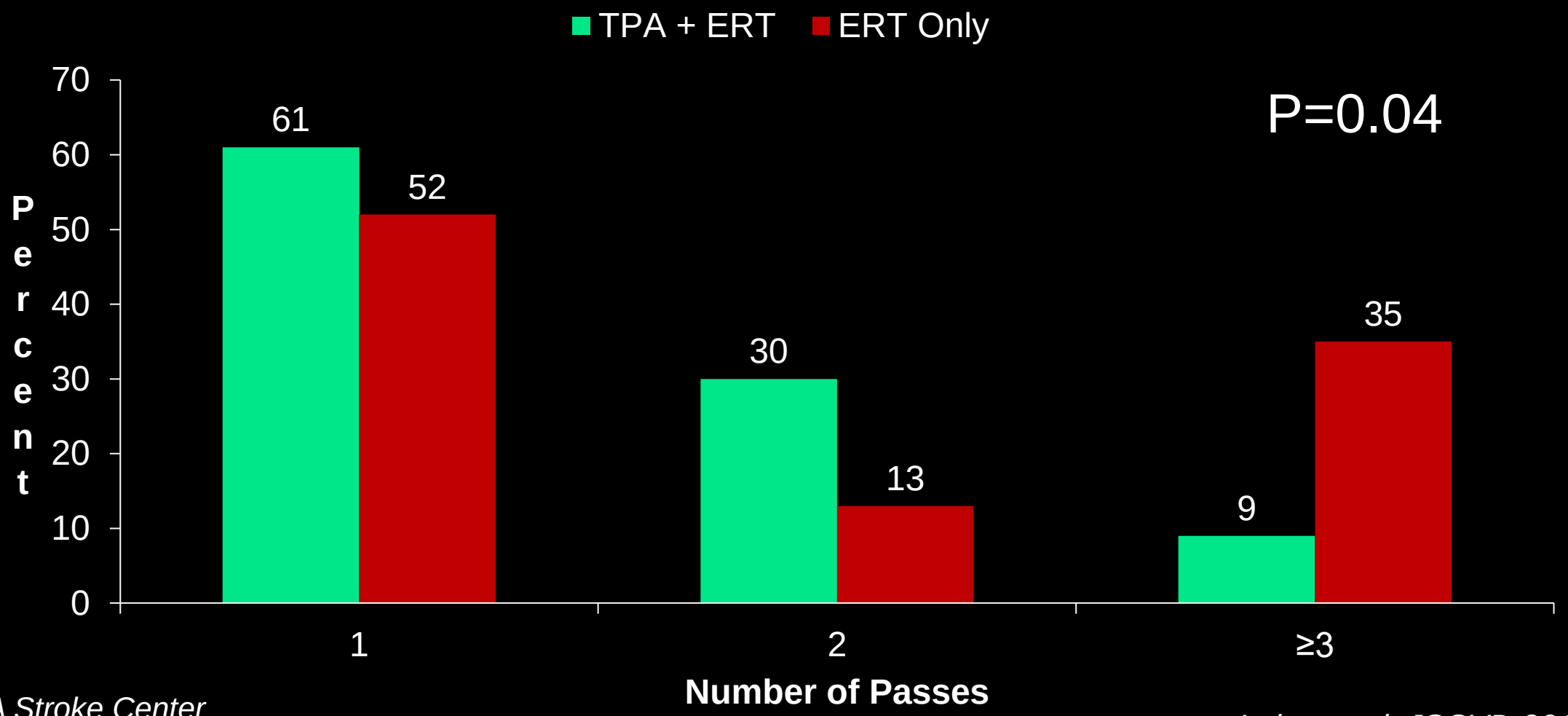
Bridging IV Lytics
Potential Benefits

IV tPA May Increase Degree of Reperfusion with ERT

- Improve distal reperfusion
  - » Clean up distal primary thrombi
  - » Clean up distal secondary thrombi dislodged by retriever/aspiration devices
- Increase responsiveness of target, proximal thrombi to mechanical removal (“conditioning”)

--Castonguay et al, Stroke 2014

Fewer Stent Retriever Passes Required in IV tPA Patients



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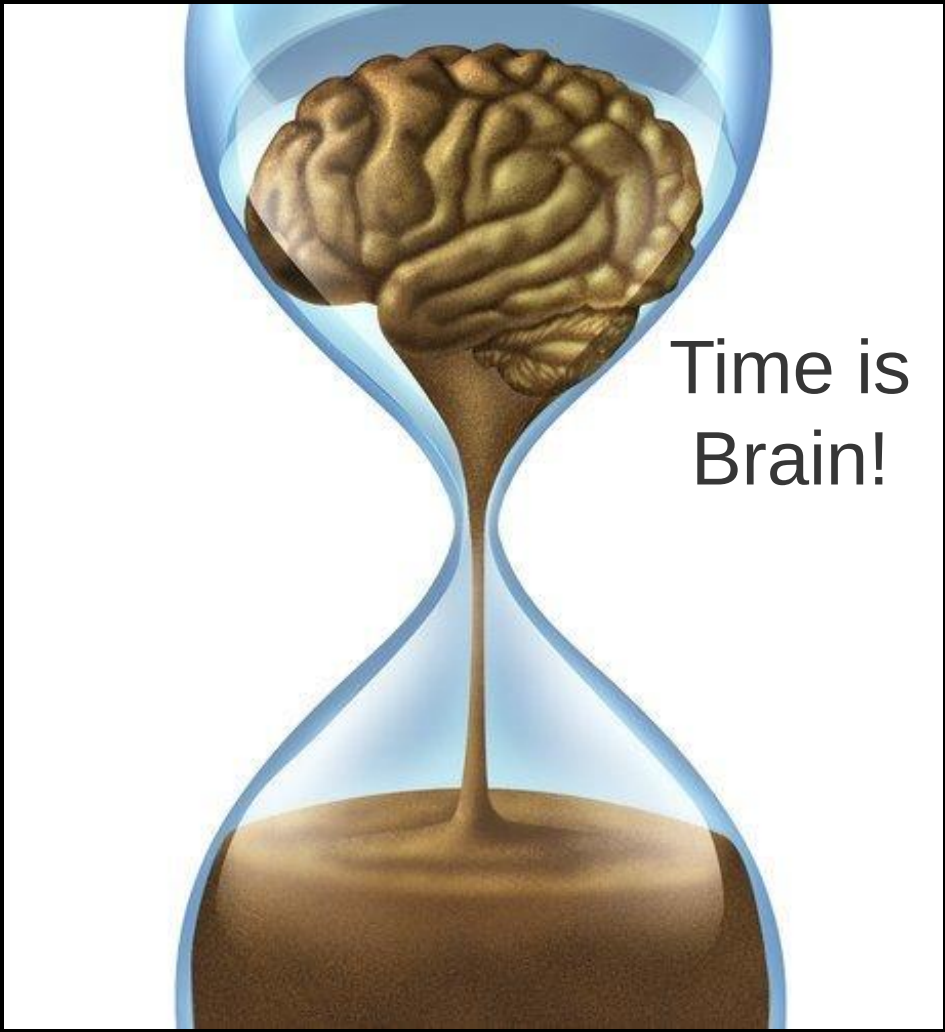
--Leker et al, JSCVD 2015

TPA Can Dissolve Clots Before Thrombectomy



- Meta-analysis of reperfusion before MT in LVO
  - » 13 studies
  - » 1561 patients
  - » Successful reperfusion before MT in 11% (95CI 7-16%)

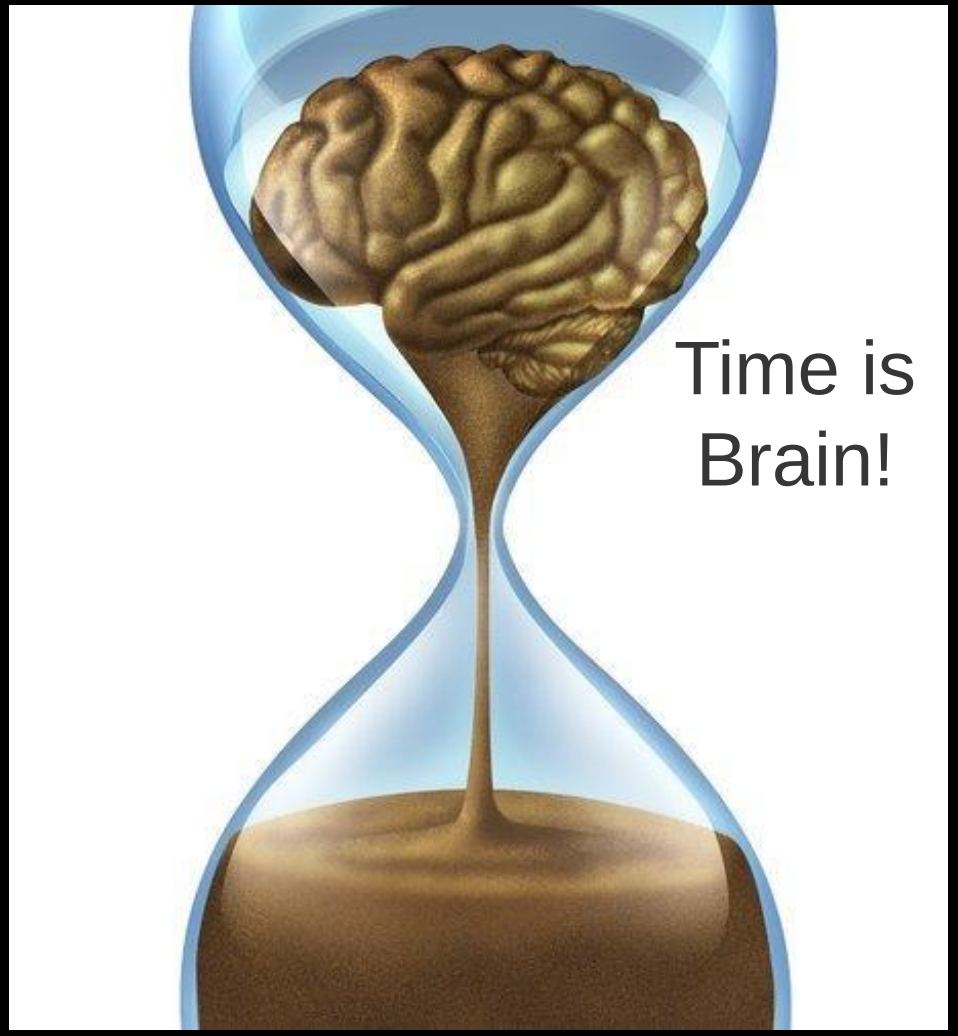
--Tsivgoulis et al, Stroke 2018

IV TPA May Increase Frequency of Reperfusion When ERT Cannot Be Pursued

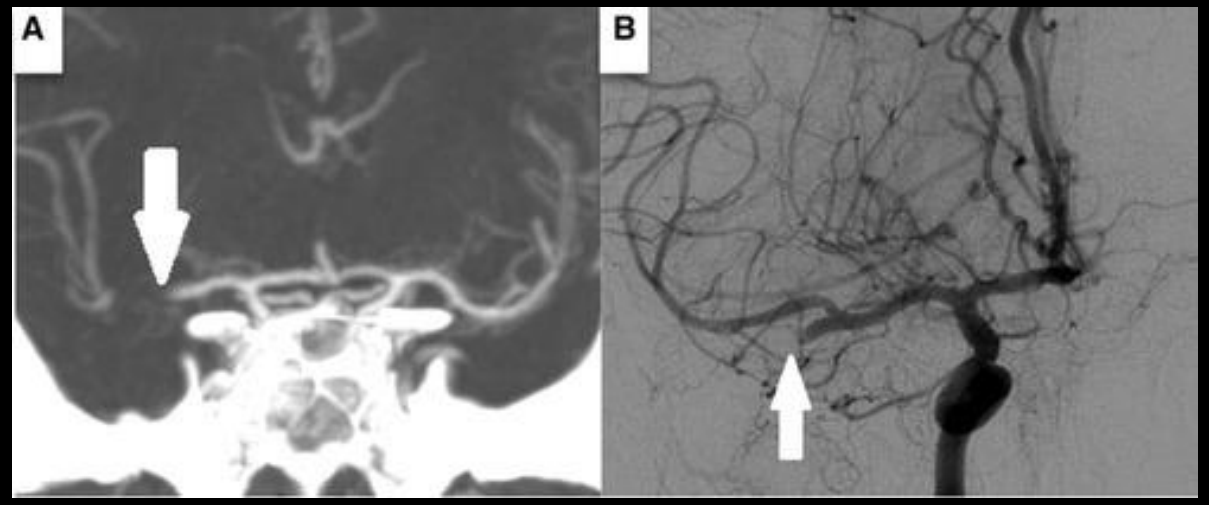
- Thrombectomy device unable to reach target occlusion
  - » Tortuous anatomy
  - » Cervical carotid occlusion/poor femoral/radial access
  - » Medical instability
    - Cardiorespiratory distress
    - Seizure
  - » Cath lab equipment failure
  - » Competing cases
  - » Interventional team roadway misadventure
  - » Interfacility/Field transfer delay
- IV tPA only hope for reperfusion
  - » ERT failure will only be known after IV tPA window closes

Bridging IV Lytics
Potential Harms

Slower Start of EVT Due to IVT Logistics



Thrombus Fragmentation with Migration to Inaccessible Artery(ies)

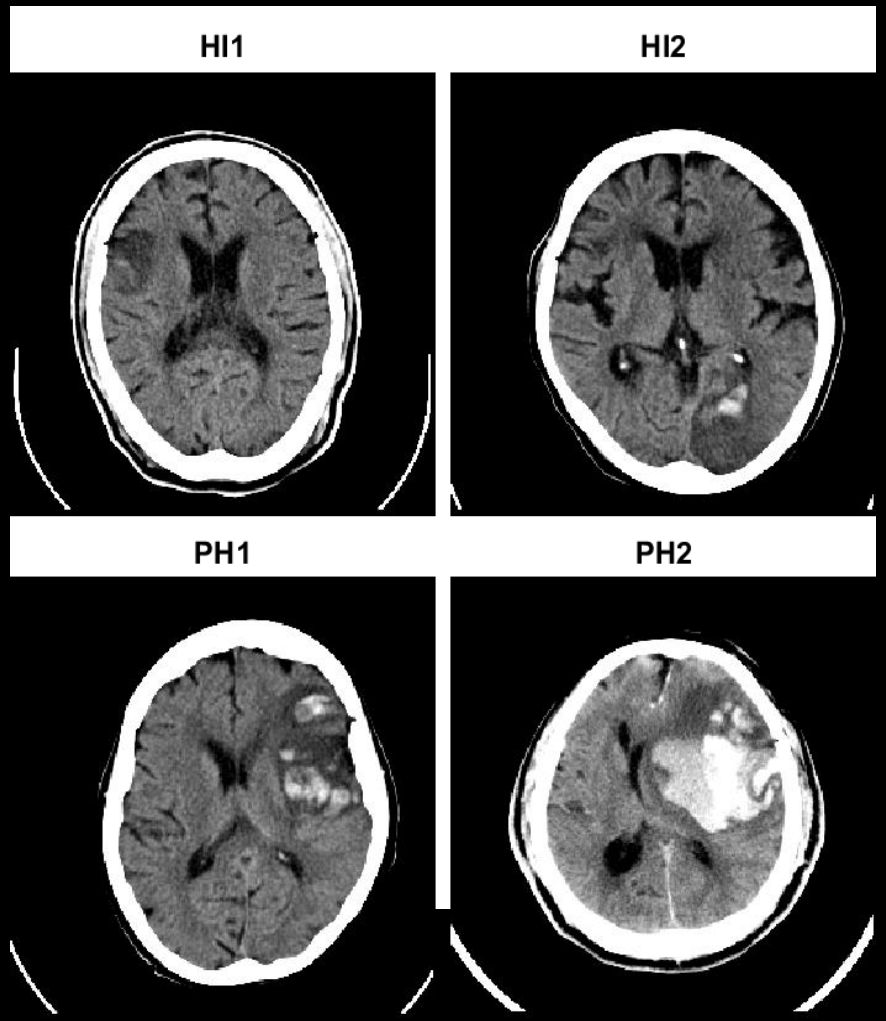


--Sporns et al, Stroke 2019

- MR CLEAN Registry
- 1349 patients
- Thrombus migration in 22%
- Migration ↑ with bridging TPA
  - » OR 2.01 (CI 1.29-3.11)
- Complete reperfusion ↓ with migration
  - » OR 0.57 (CI 0.42-0.78)

--Alves et al, Stroke 2019

Increased Symptomatic Intracranial Hemorrhage



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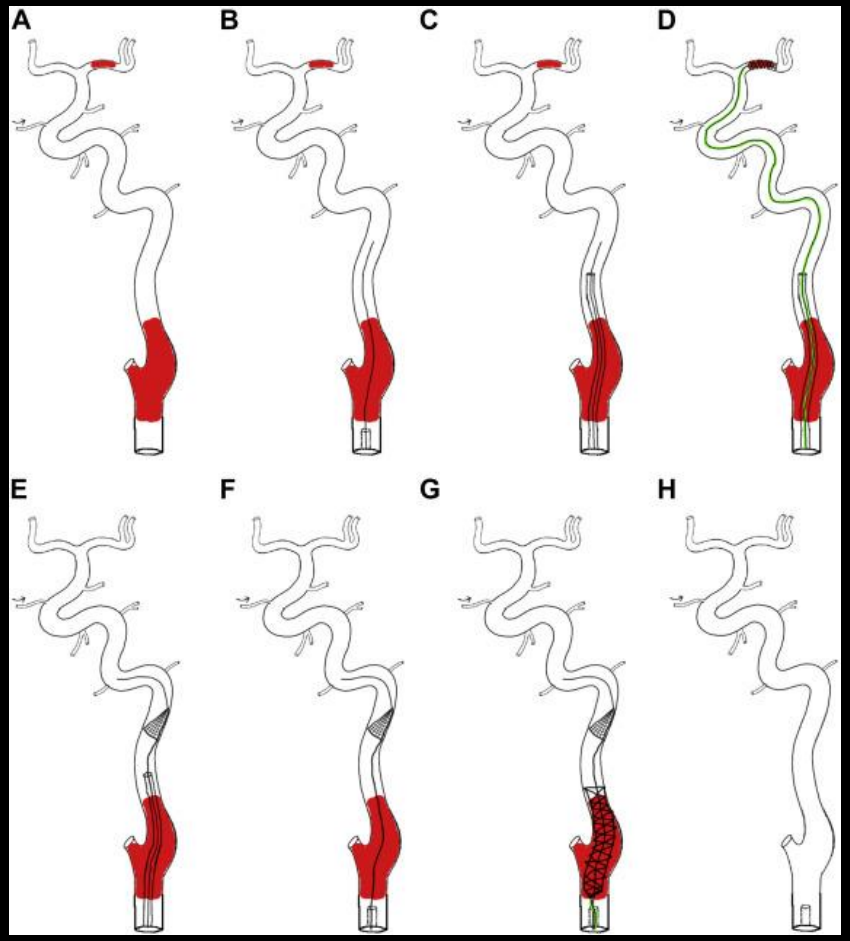
--Ong et al, Drug Des Devel Ther 2017

Inability to Protect Acute Angioplasty/Stents with Double Antiplatelet Rx for 1st 24h

- Indications for concomitant angioplasty / stent with EVT
  - » Tandem disease
    - Cervical arthero carotid stenosis and intracranial occlusion



--Chen W-H et al. World Nsurg 2018

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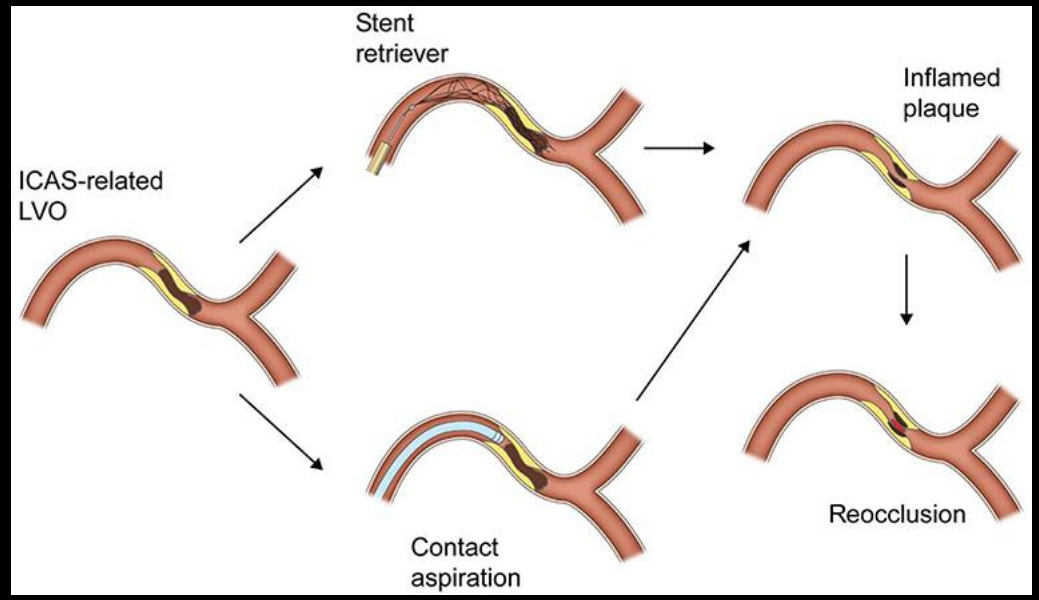
- Indications for concomitant angioplasty / stent with EVT
  - » Tandem disease
    - Cervical arthero carotid stenosis and intracranial occlusion
  - » Intracranial atherosclerosis
    - With *in situ* thrombosis
  - » Dissection



--Park H et al. W-H et al. Front Neurol 2019

RCTs

Features of Reported Bridging vs Direct EVT Trials

Trial	Region	Size	TPA Dose	Analytic Design	Age	NIHSS	Onset to Randomizaton	Door to Lytic	Lytic to Puncture
DIRECT MT	China	656	0.9 mg/kg	Non-Inferiority (then superiority)	69	17	2h 52m	59m	24m
DEVT	China	234	0.9 mg/kg	Non-Inferiority (then superiority)	70	16	2h 49m	61m	40m
SKIP	Japan	204	0.6 mg/kg	Non-Inferiority (then superiority)	75	18	2h 13m	50m	8m
MR CLEAN NO IV	Europe	539	0.9 mg/kg	Superiority (then non-Inferiority)	72	16	1h 34m		37m

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Total 1633

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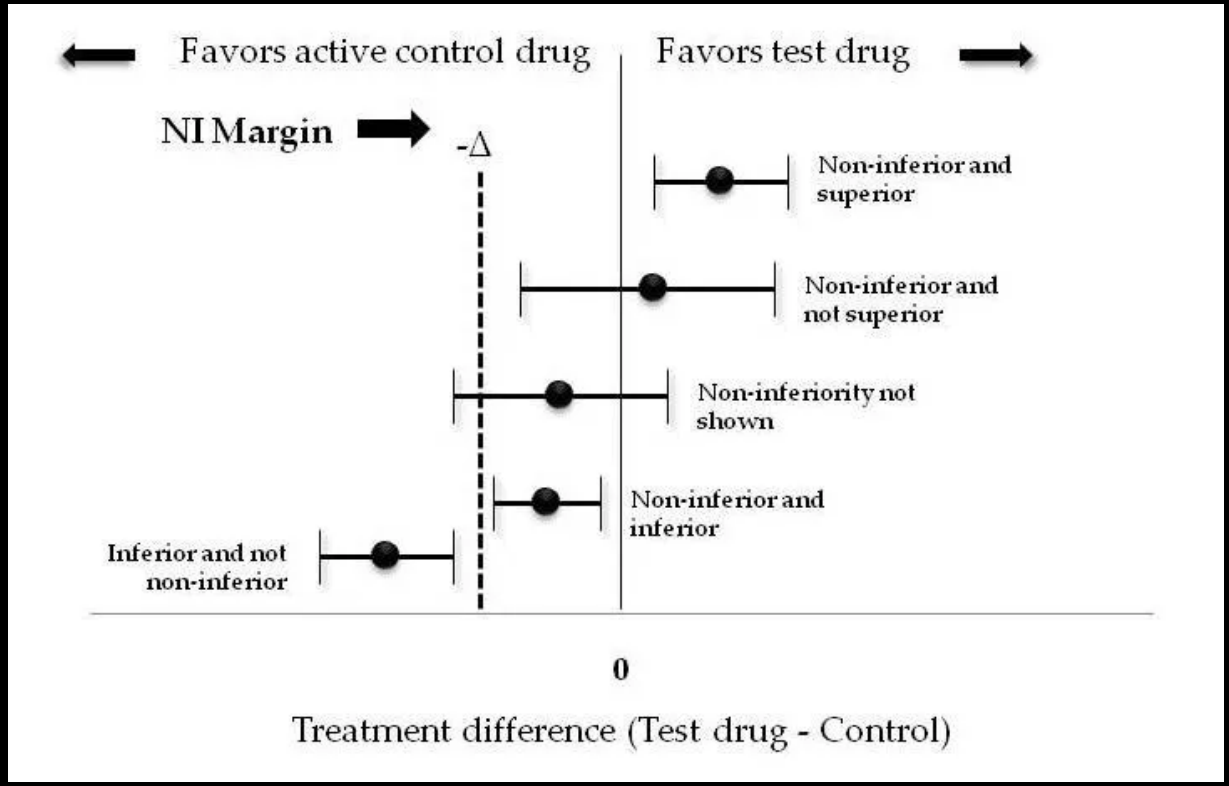
Background: Non-Inferiority Margins (NIMs)

- Selection of NIM crucial in testing for NI
- Methods
  - » MCID: Indistinguishability
  - » Fixed margin: at least a substantial fraction of benefit



Background: Two Approaches to Selecting Non-Inferiority Margins (NIMs)

	Minimal Clinically Important Difference	Fixed Margin
Seeks to Demonstrate New Rx	Delivers results at least indistinguishable from standard Rx	Delivers at least a substantial fraction of the benefit of standard Rx
Sample Size Required If Tx Actually Equal	Very large	Moderate
Current terminology	Non-Inferiority Margin	Non-Inferiority Margin
Better terminology	Non-Inferiority Margin	Reasonably Comparable Margin

--Schumi J, Wittes JT, Trials 2011; Rothmann M et al, Stat Med 2003; FDA Guidance, 2016 Lin CJ, Saver JL, Stroke 2019; Saver JL, JAMA 2021

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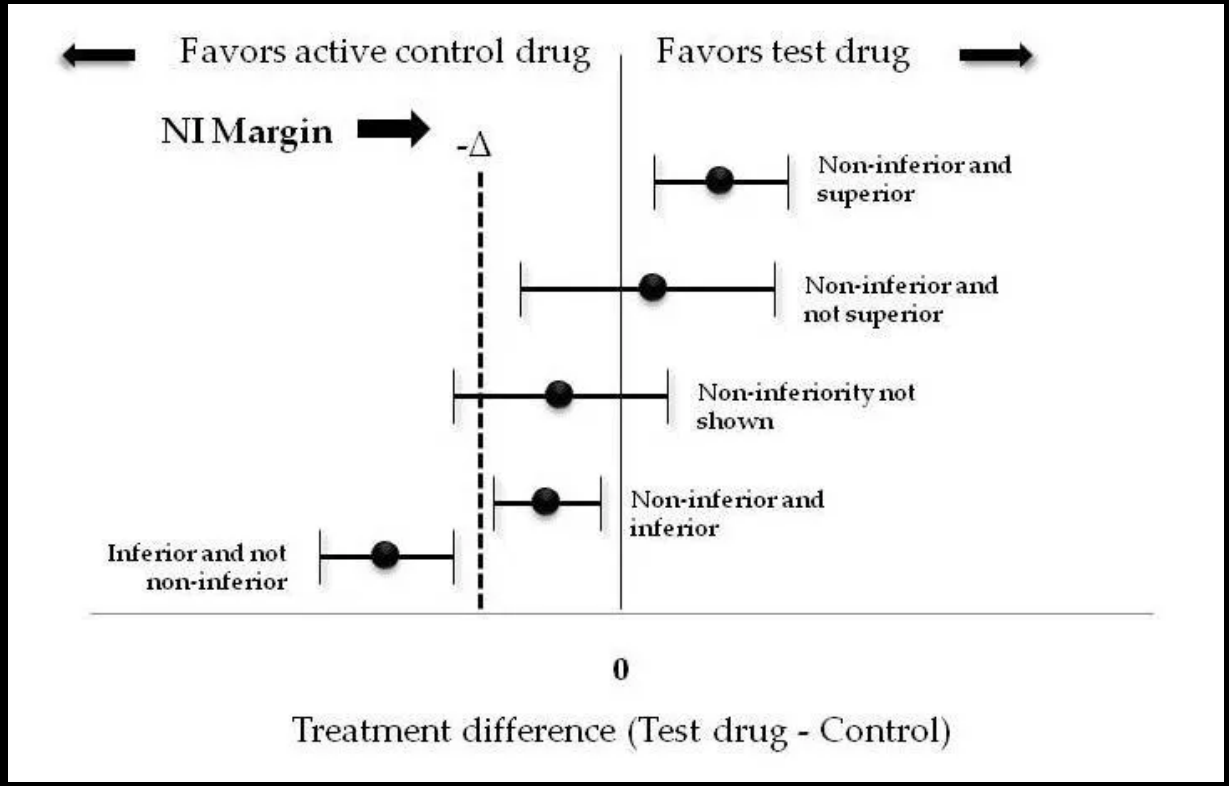

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- Selection of NIM crucial in testing for NI
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  - » MCID: Indistinguishability
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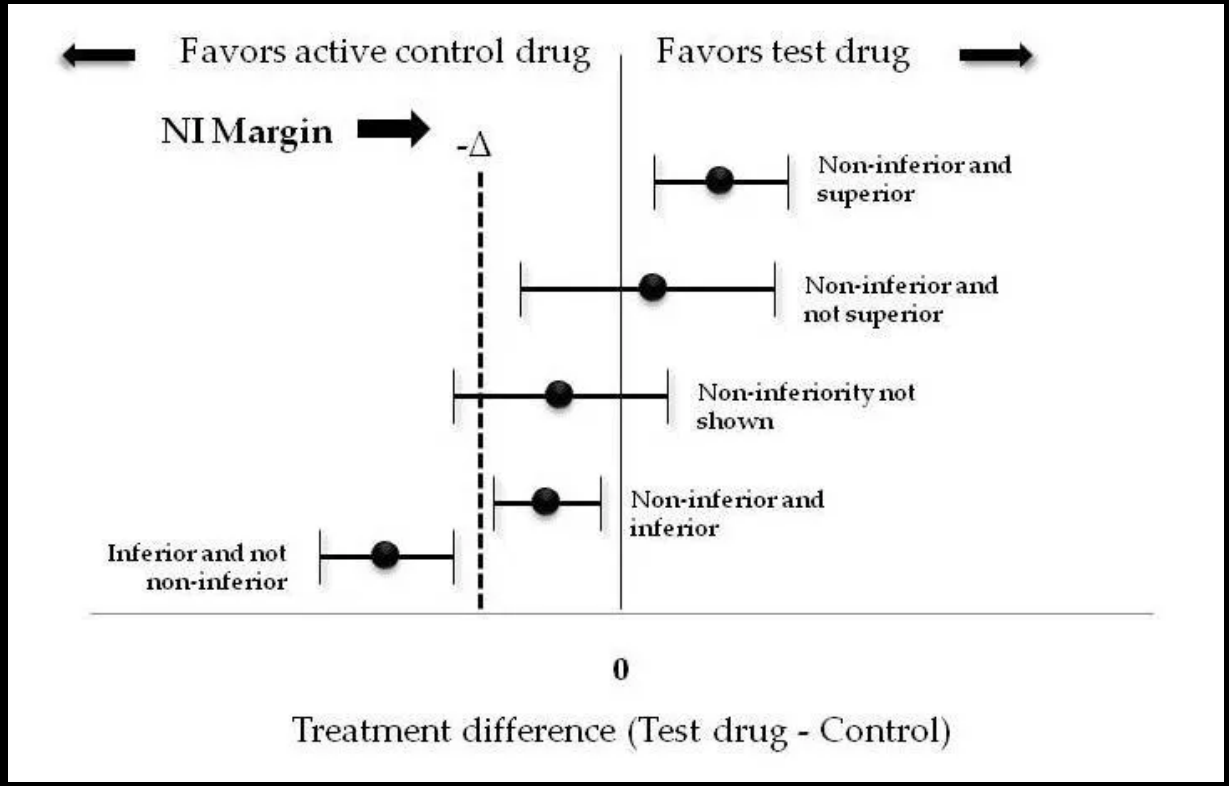
- For dichotomized mRS
  - » -15.0% (COMPASS)[1]
  - » -6.5% (ENCHANTED)[2]
  - » -5.0% (Expert survey w/ potential anchoring bias)[3]
  - » -1.3% (Expert survey w/o potential anchoring bias)[4]



[1]Turk et al, Lancet 2019; [2]Anderson et al, NEJM 2016; [3]Savitz et al, CVD 2008; [4] Cranston et al, Stroke 2017

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- Method
  - » MC
  - » Fix
    frac
- For dic
  - » -15
  - » -6
  - » -5
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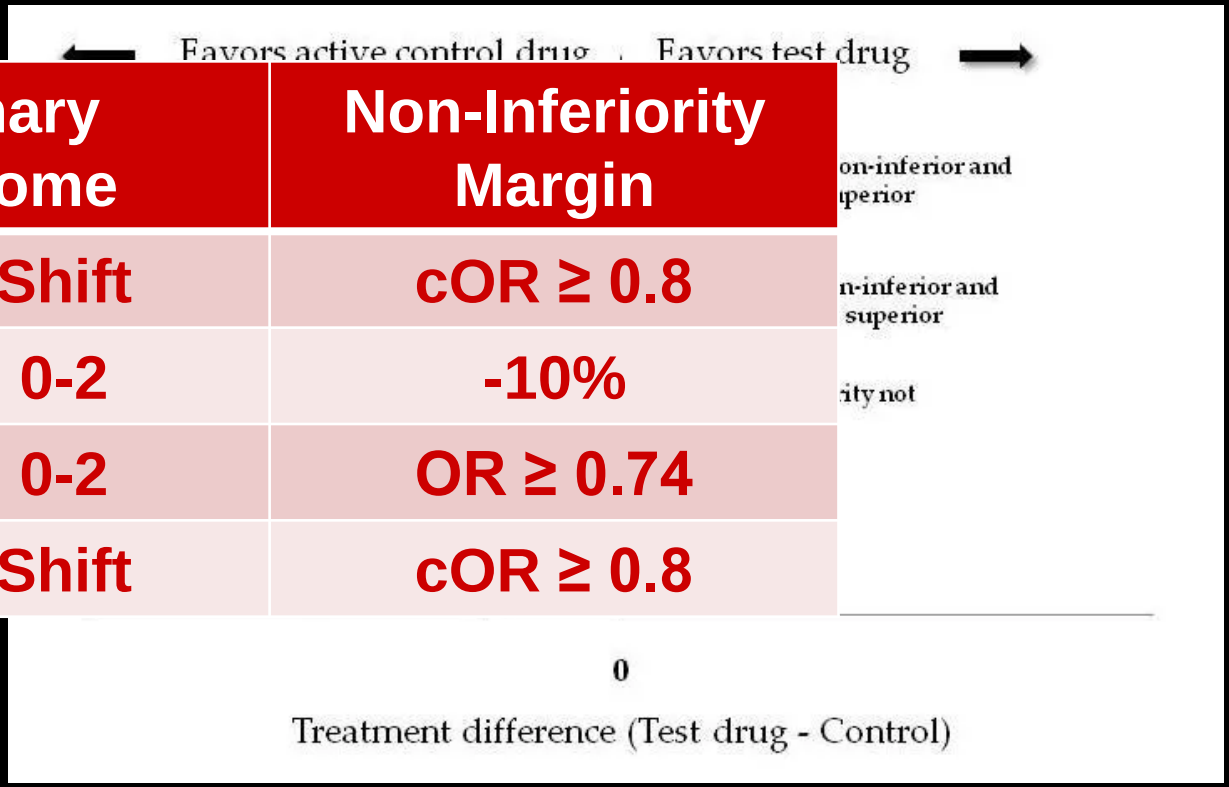
Trial	Primary Outcome	Non-Inferiority Margin
DIRECT MT	mRS Shift	cOR ≥ 0.8
DEVT	mRS 0-2	-10%
SKIP	mRS 0-2	OR ≥ 0.74
MR CLEAN	mRS Shift	cOR ≥ 0.8



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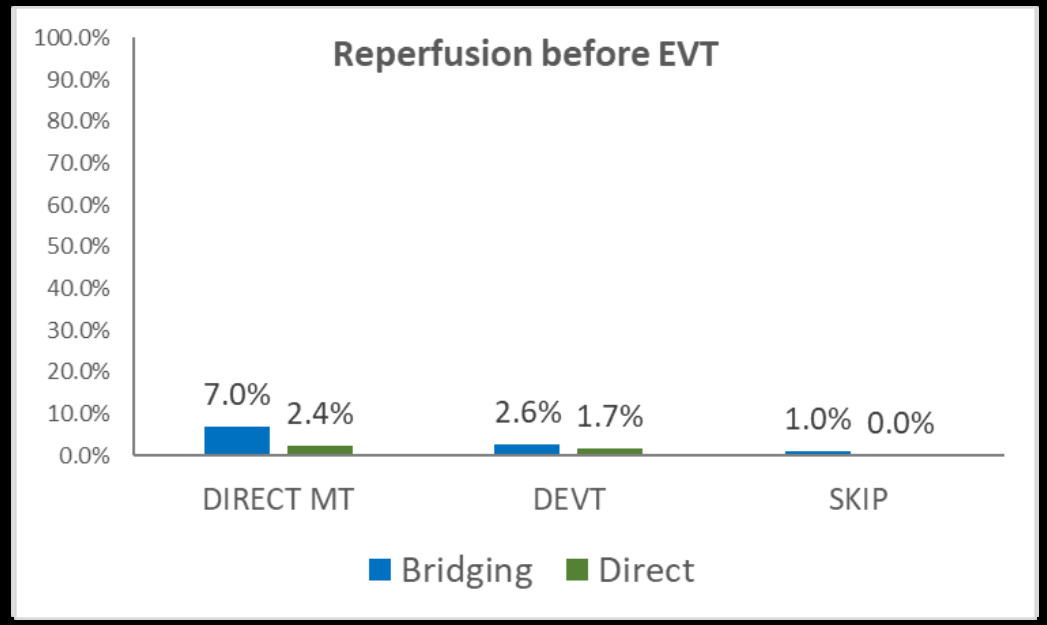
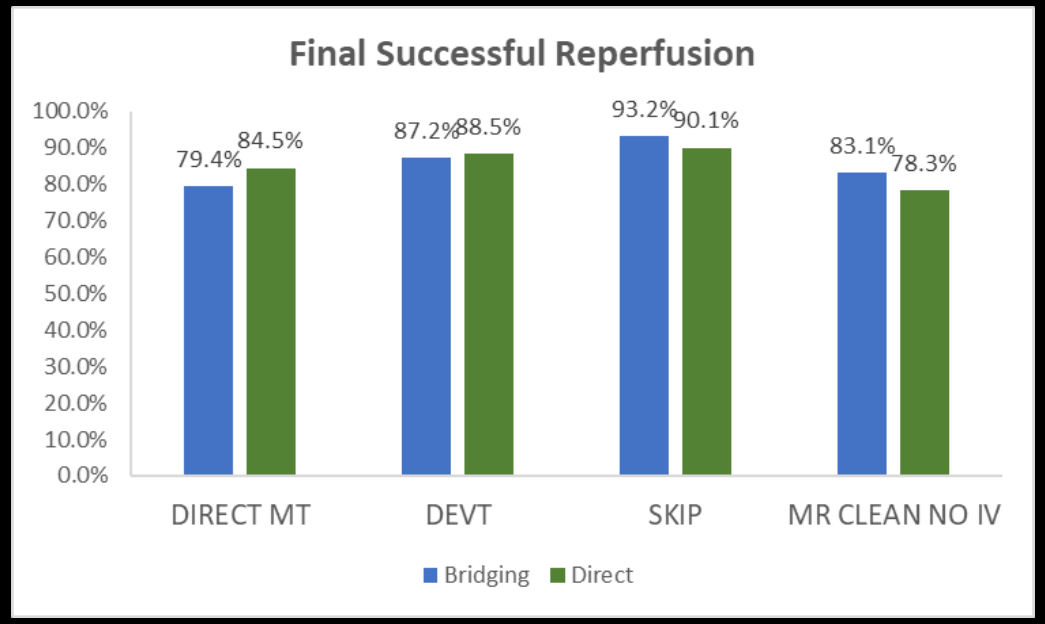
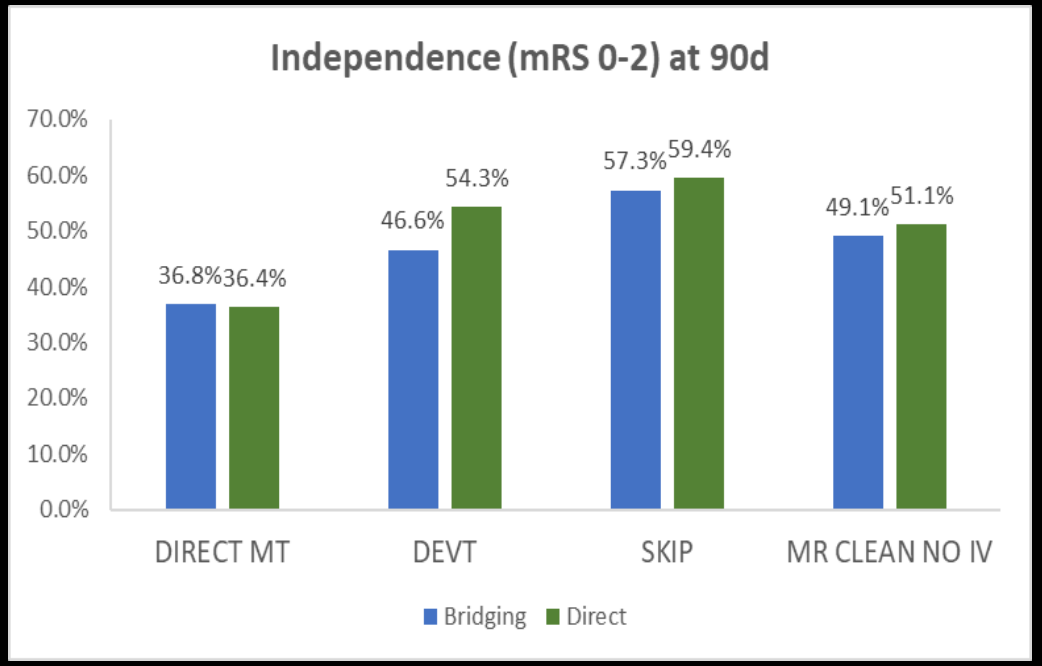
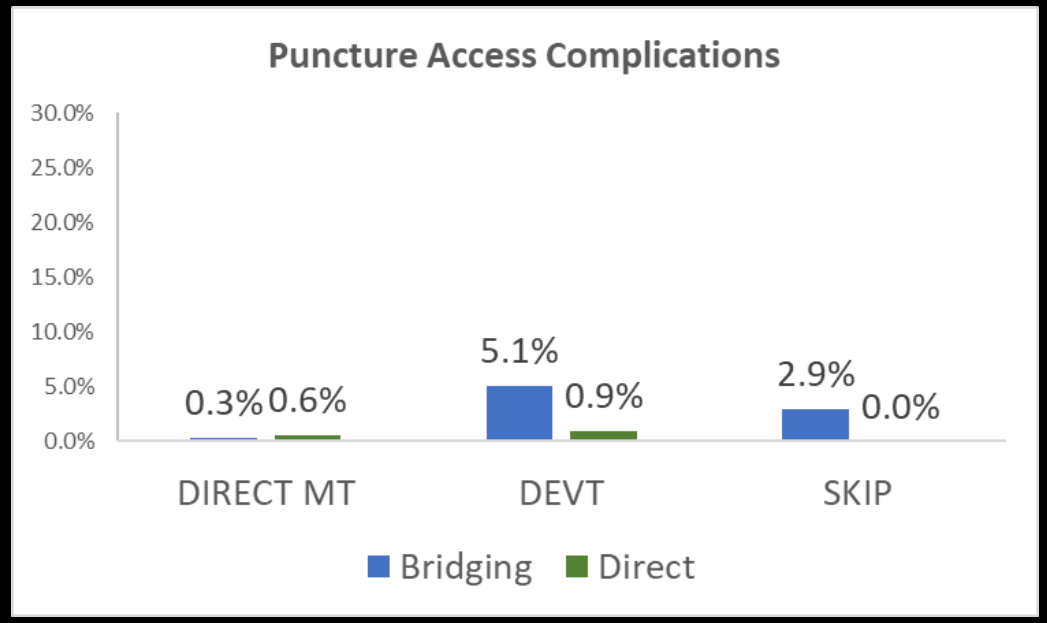
Efficacy Reperfusion and Clinical Outcomes

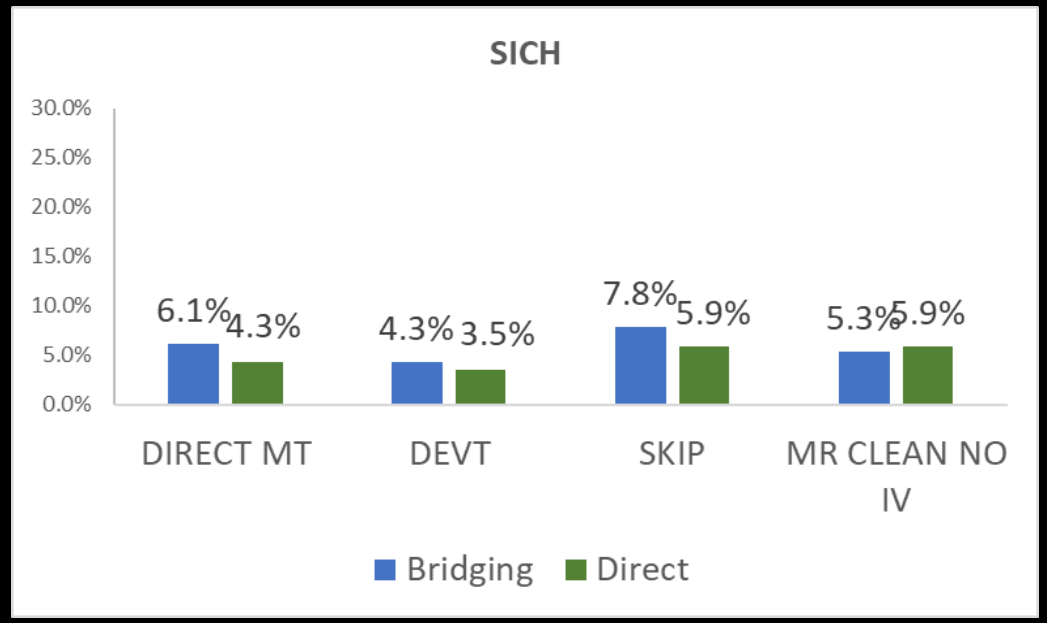


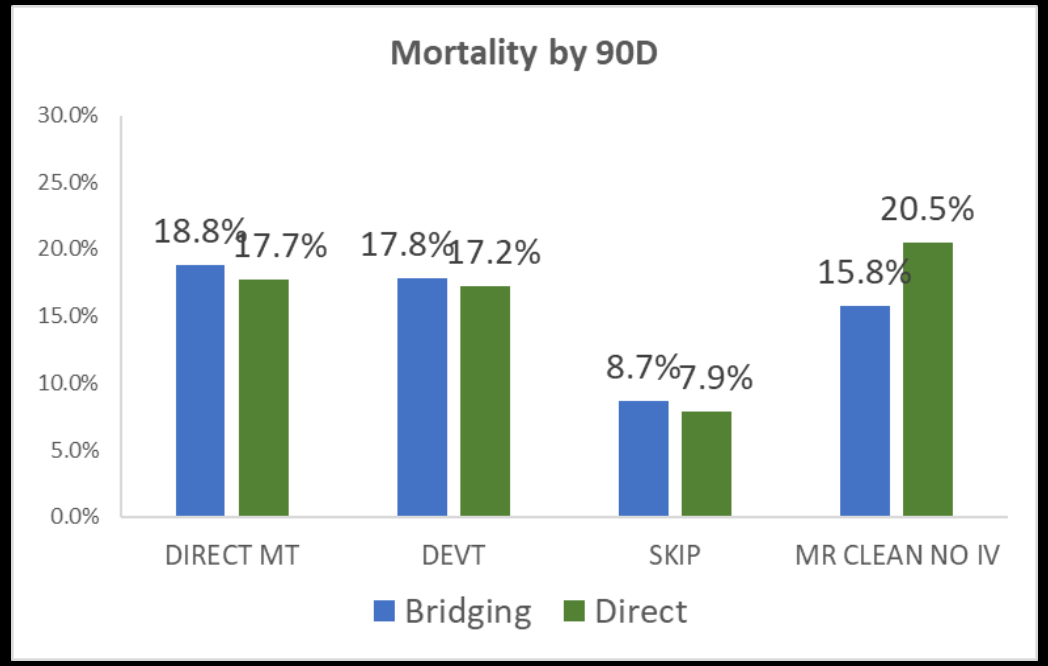




Safety Outcomes





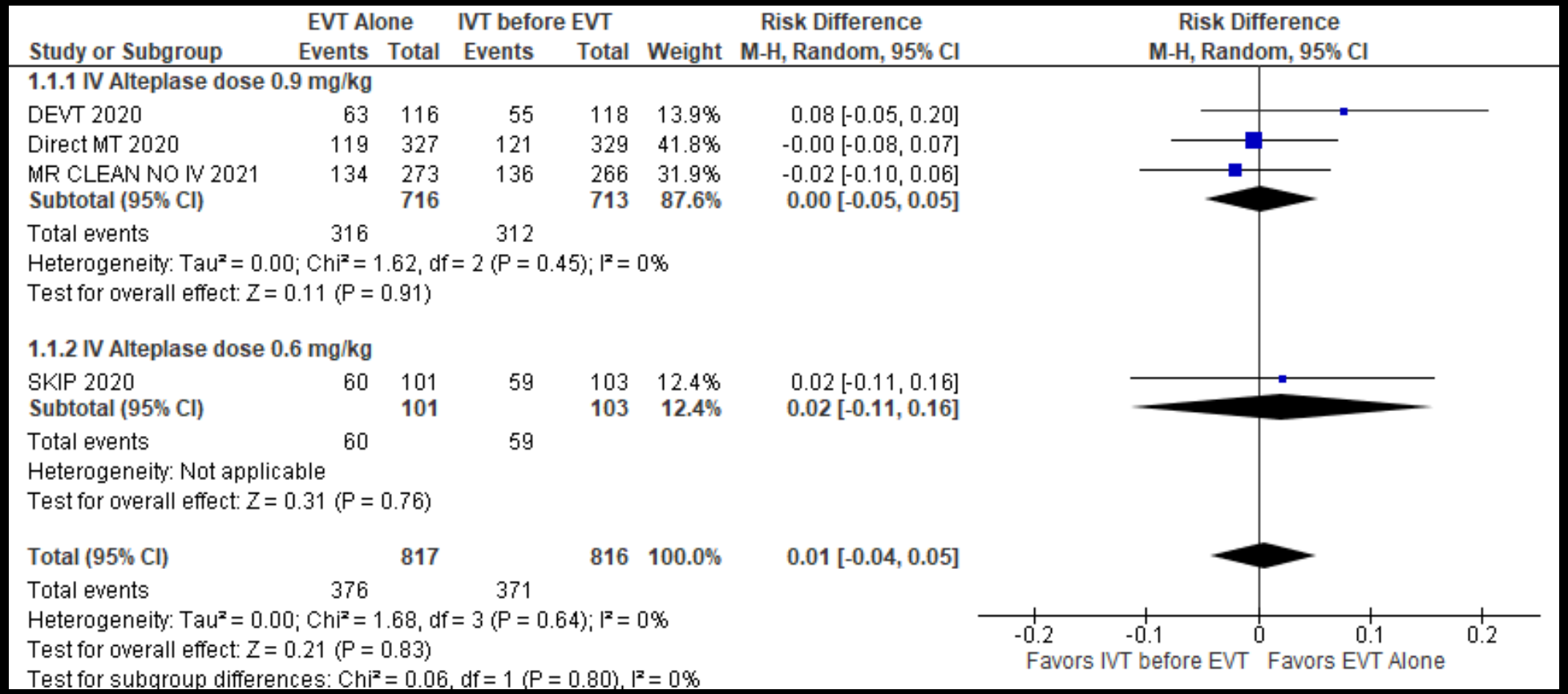


Primary Efficacy Results of Bridging vs Direct EVT Trials

Trial	Primary Outcome	Non-Inferiority Margin	Actual Outcome	P value for Non-Inferiority
DIRECT MT	mRS Shift	cOR ≥ 0.8	cOR 1.07 (0.81 to 1.40)	0.04
DEVT	mRS 0-2	-10%	-7.7% (−5.1% to ∞)	0.003
SKIP	mRS 0-2	OR ≥ 0.74	1.09 (0.63 to ∞)	0.18
MR CLEAN NO IV	mRS Shift	cOR ≥ 0.8	cOR 0.88 (0.65 to 1.19)	NS

Study-Level Meta-Analysis of All 4 RCTs[1]

Independence (mRS 0-2) at 90 days



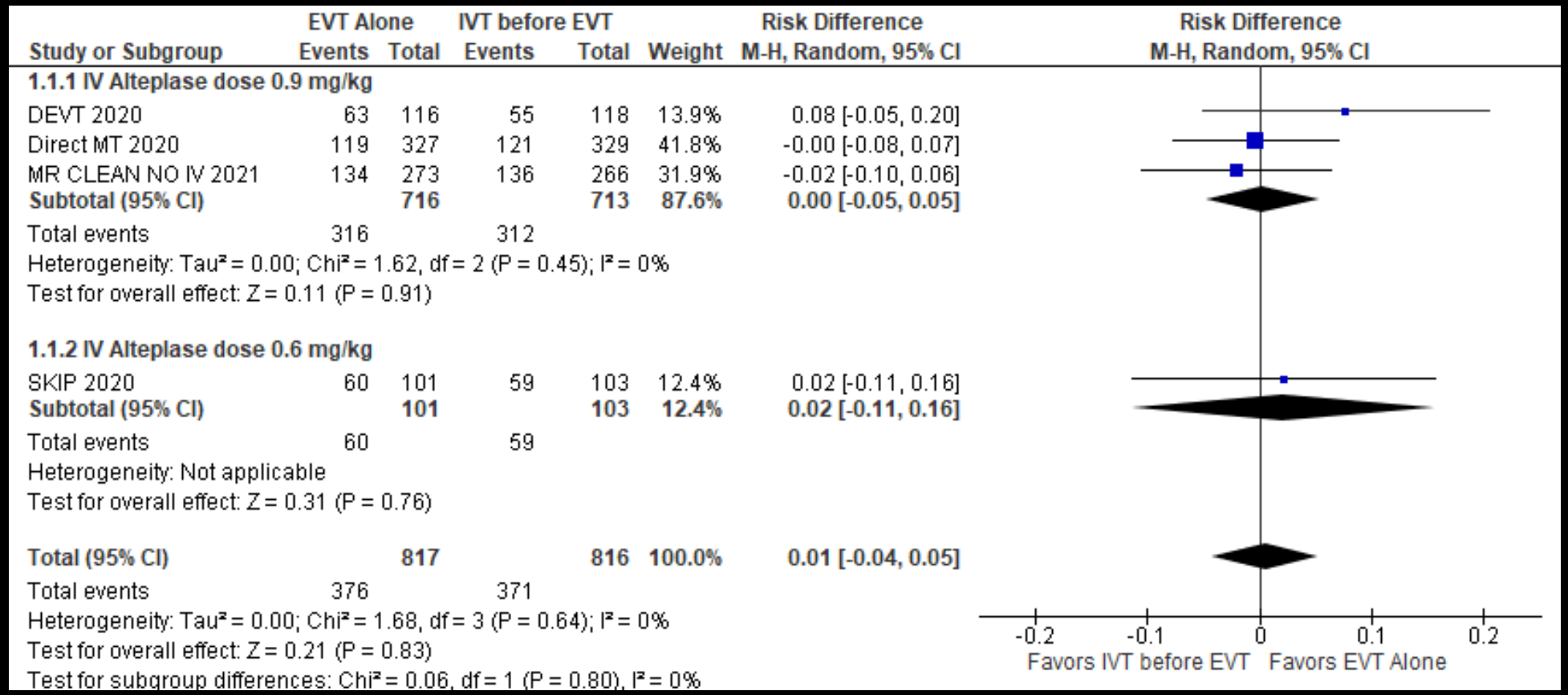
Study or Subgroup	EVT Alone Events	EVT Alone Total	IVT before EVT Events	IVT before EVT Total	Weight	Risk Difference M-H, Random, 95% CI
1.1.1 IV Alteplase dose 0.9 mg/kg						
DEVT 2020	63	116	55	118	13.9%	0.08 [-0.05, 0.20]
Direct MT 2020	119	327	121	329	41.8%	-0.00 [-0.08, 0.07]
MR CLEAN NO IV 2021	134	273	136	266	31.9%	-0.02 [-0.10, 0.06]
Subtotal (95% CI)		**716**		**713**	**87.6%**	**0.00 [-0.05, 0.05]**
Total events	316		312			
Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.1.2 IV Alteplase dose 0.6 mg/kg						
SKIP 2020	60	101	59	103	12.4%	0.02 [-0.11, 0.16]
Subtotal (95% CI)		**101**		**103**	**12.4%**	**0.02 [-0.11, 0.16]**
Total events	60		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**817**		**816**	**100.0%**	**0.01 [-0.04, 0.05]**
Total events	376		371			
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 3 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.83)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%						

Direct vs Bridging: 46.0% vs 45.4%

Risk Difference: 1% (CI -4% to 5%)

[1]Saver JL, FDA Journal Club, April 2021

Among 100 LVO Stroke Patients, How Many Fewer 90d mRS 0-2 Outcomes with Direct c/w Bridging is Acceptable to You?



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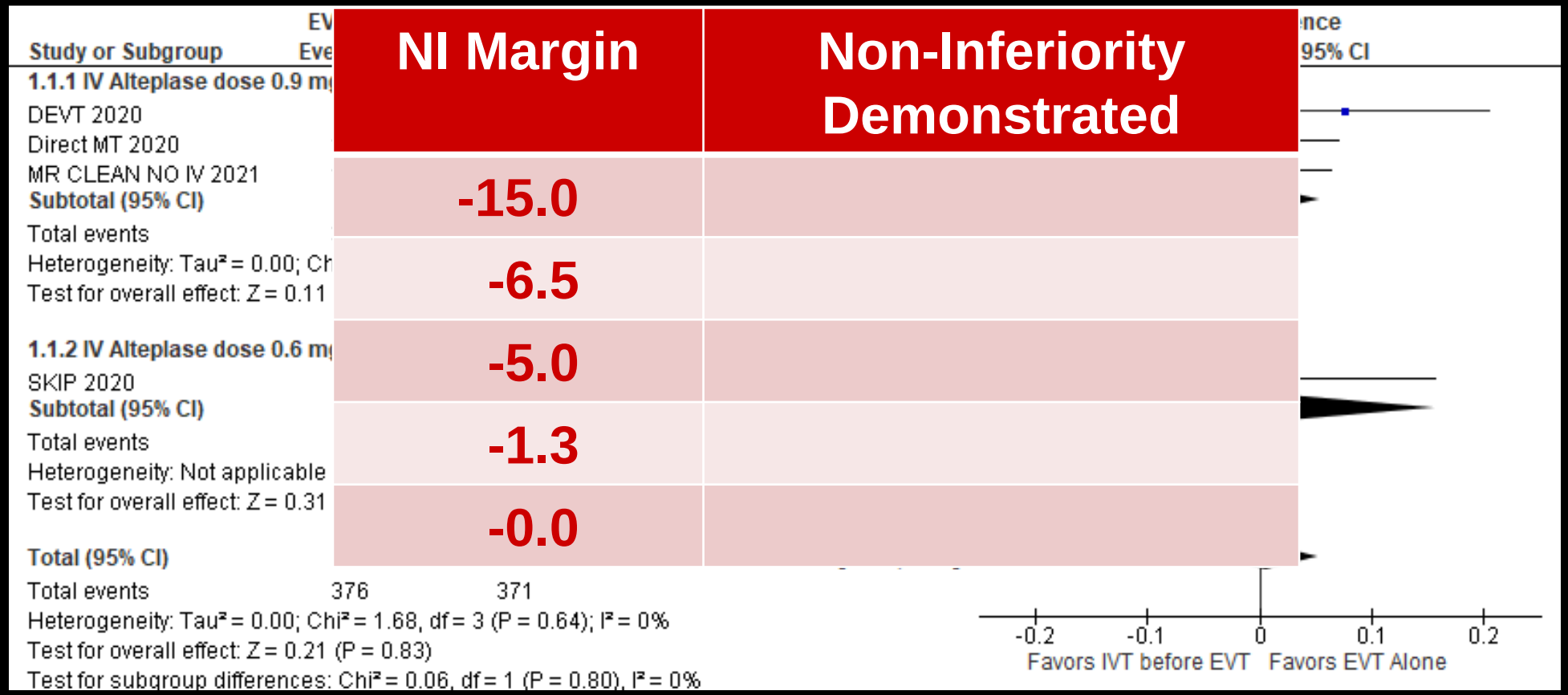
[1]Saver JL, FDA Journal Club, April 2021

Among 100 LVO Stroke Patients, How Many Fewer 90d mRS 0-2 Outcomes with Direct c/w Bridging is Acceptable to You?



NI Margin	Non-Inferiority Demonstrated
-15.0	
-6.5	
-5.0	
-1.3	
-0.0	

Direct vs Bridging: 46.0% vs 45.4%

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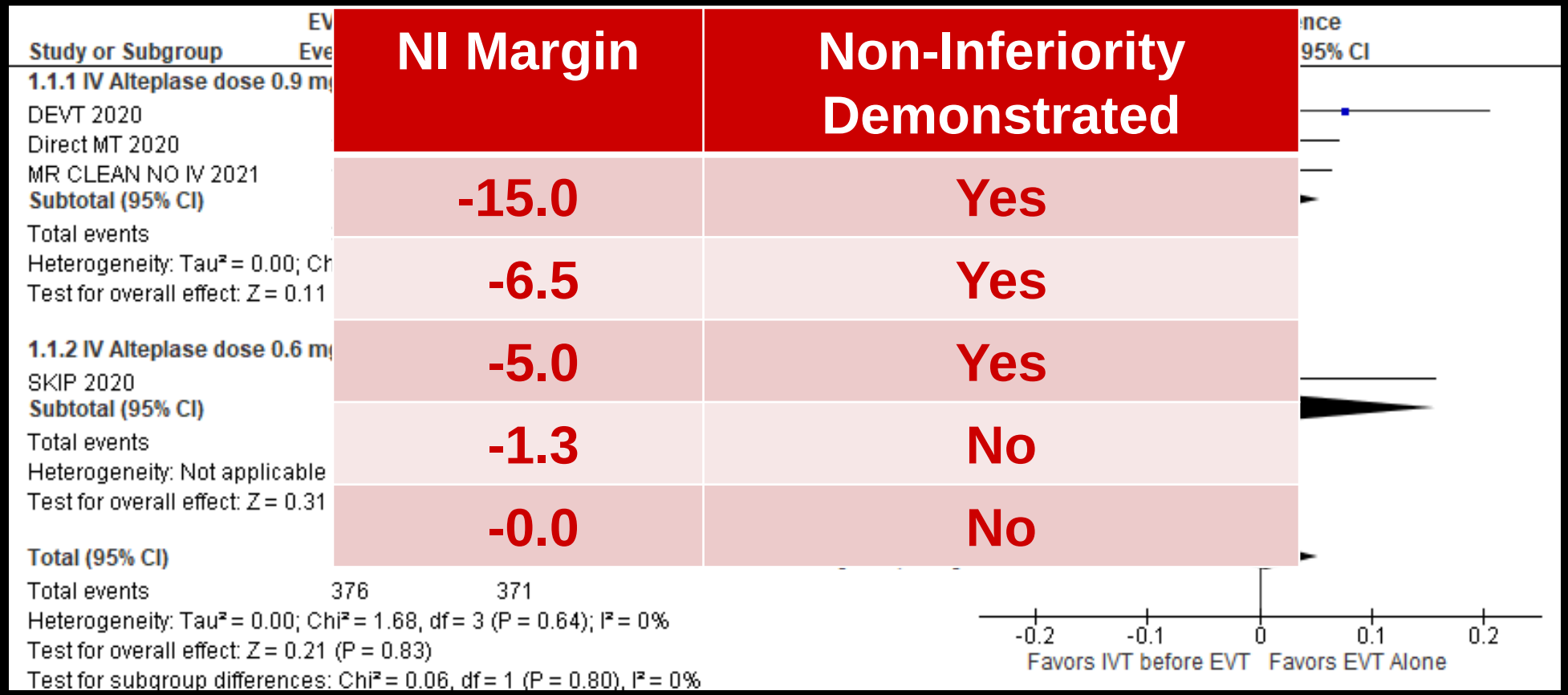

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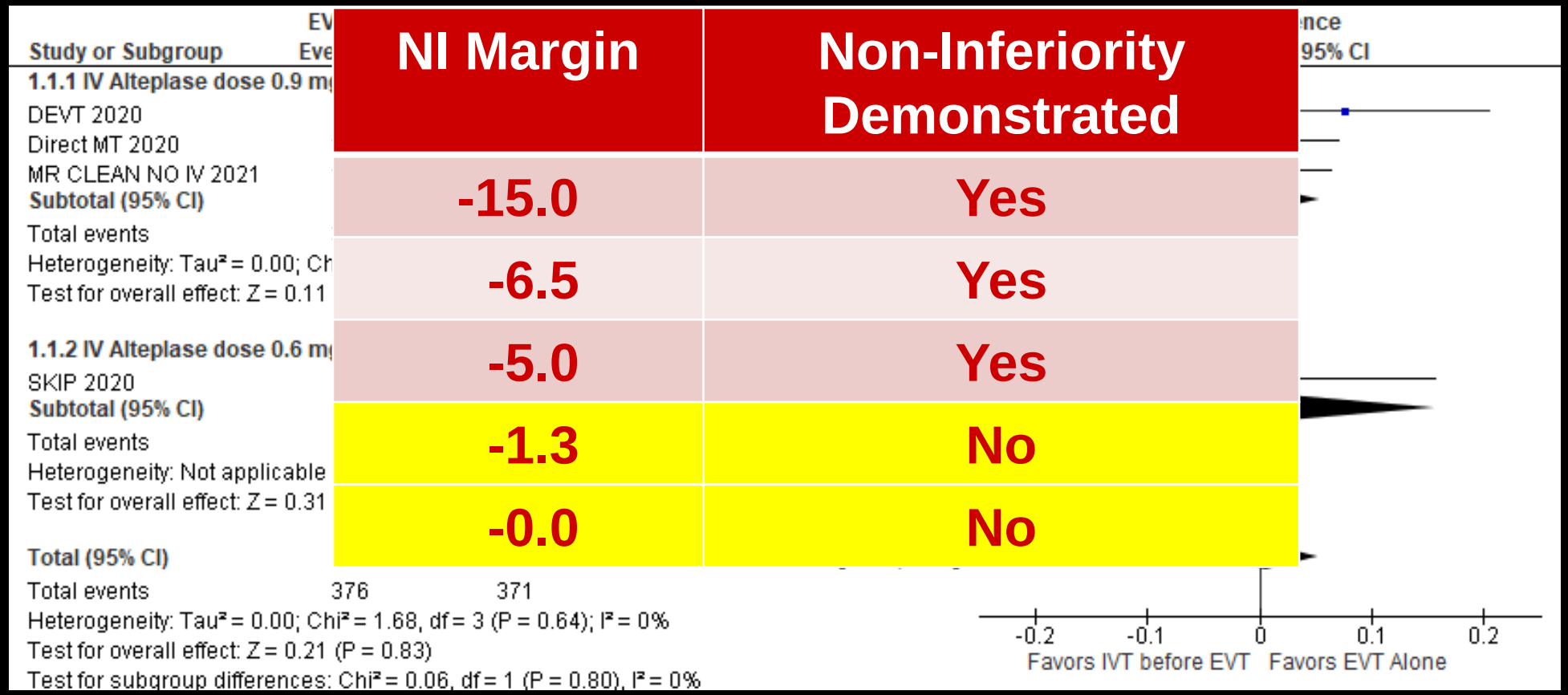

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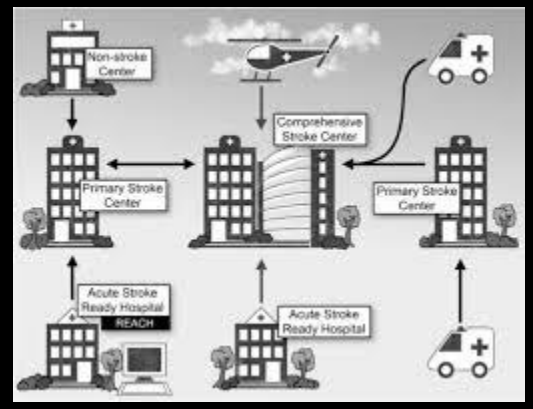
Features of Ongoing Bridging vs Direct EVT Trials

Trial	Region	Size	Primary Outcome	Design	NI Margin
SWIFT DIRECT	Europe, Canada	404	mRS 0-2	Non-Inferiority (then superiority)	-12%
DIRECT-SAFE	Australia, NZ, Asia, Europe	780	mRS Shift + mRS 0-2	Non-Inferiority (then superiority)	?

Clinical Implications

Definitely Continue to Use Bridging Lytics
When EVT Will Be Delayed or Uncertain

- Initial nonthrombectomy hospital presentation
- Neurointerventional team/suite not immediately available
- Ipsilateral chronic cervical carotid occlusion
- Excessive aortocervical arterial tortuosity
- Known difficult arterial access



--Gory B, et al. Stroke 2017; Hasan et al, JNS 2018; Ctisus 2016; Saver + Odeoye, JAMA 2021

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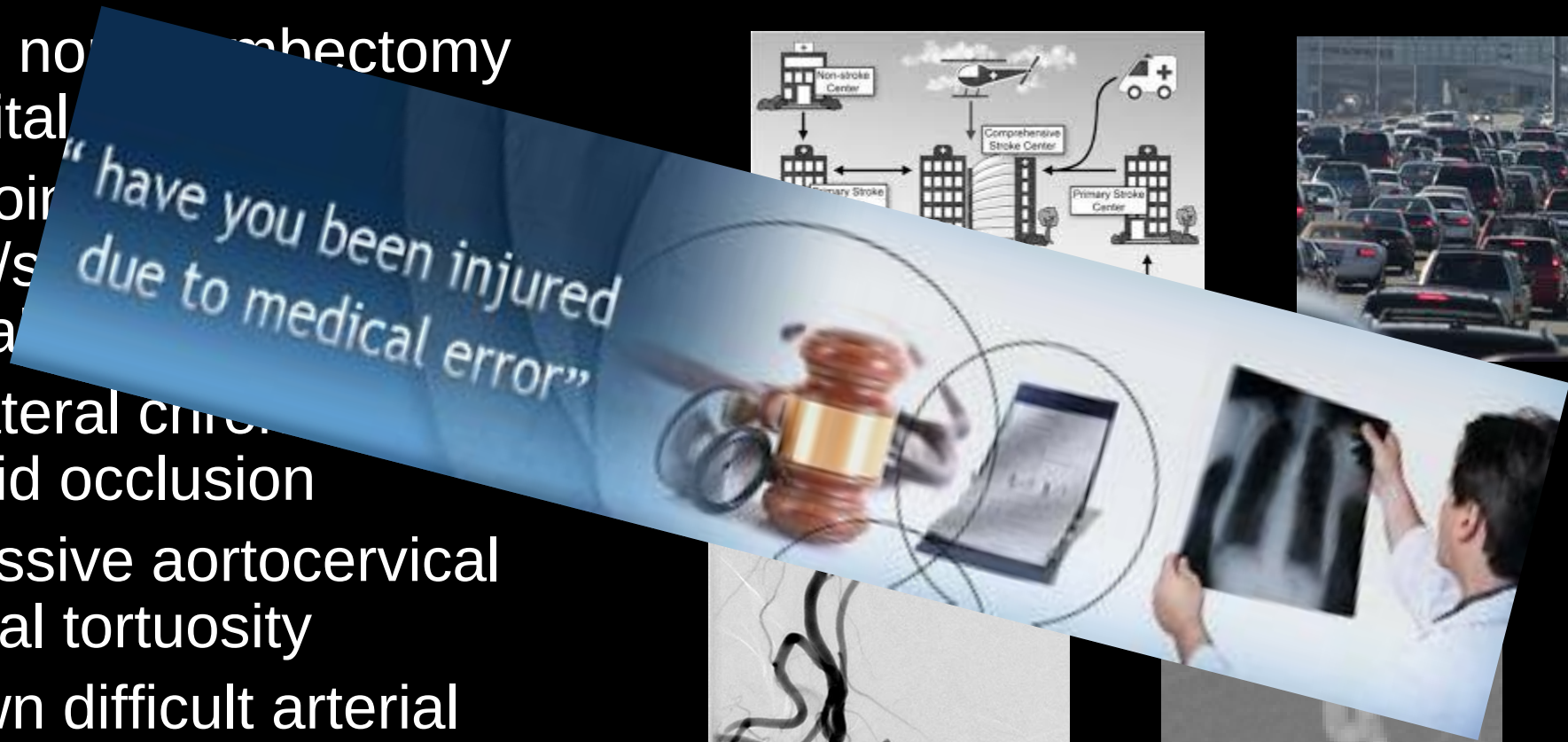

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Nuanced, Tailored Decision-Making

Feature	Favors Bridging	Favors Direct
Thrombus Responsiveness		
Hyperdense/SVS Artery Sign	Present	Absent
Thrombus Perviousness on CTA	High	Low
Clot Burden	Low (e.g. M2)	High (e.g. ICA)
First 60 Minutes (e.g. MSU)	Yes	No
Increased Bleeding Risk		
Cervical/ICAD (Possible Angioplasty/Stent, DAPT)	No	Yes
Multiple Cerebral Microbleeds	No	Yes
Extensive Leukoaraoisis	No	Yes
Large Core	No	Yes

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Bridging vs Direct: The Next Round

Bridging - Mobile Stroke Units

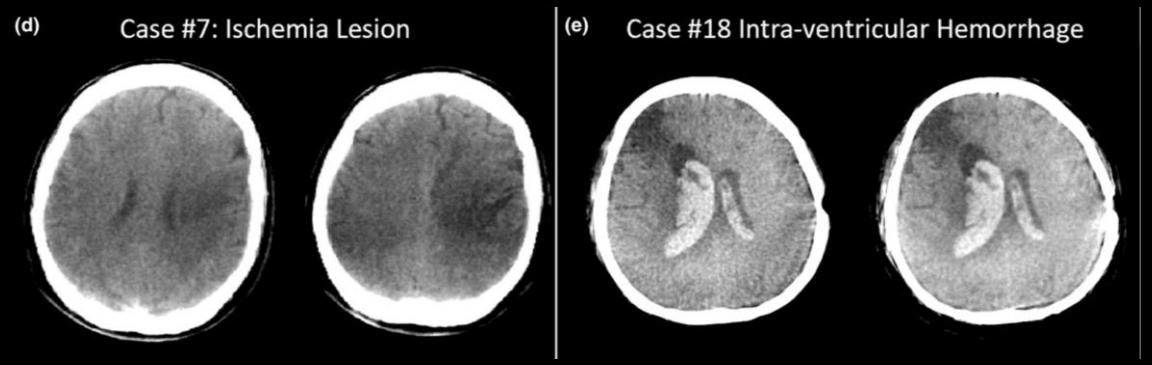
- TPA <60m in 1/3
- Higher reperfusion rate

Bridging – Better Lysis

- New Lytics, e.g TNK
- TPA+G2P3i, TPA+DTI

Direct – Direct to Angio

- Cone Beam CT on cath table
- Shorter door-to-puncture



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