Precision Medicine in Practice

Identifying the Population Responsive to EVT: Bayesian Modeling in the STEP Platform Trial

Amy M Crawford, PhD

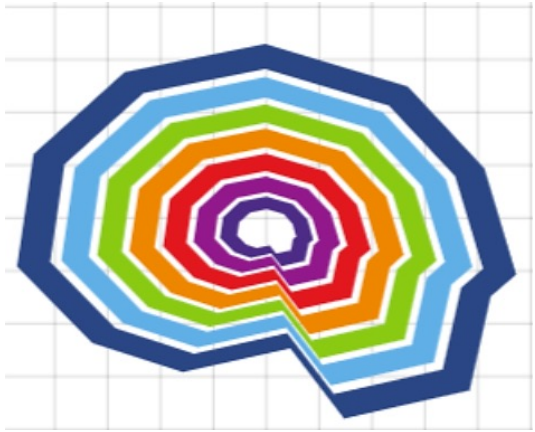
Bayes 2024

Rockville, MD

23-25 October 2024

Berry Consultants

Statistical Innovation



STEP

StokeNet Thrombectomy Endovascular Platform

Optimize the care of patients with acute ischemic stroke due to large or medium vessel occlusions.

Collaborators

Berry Consultants

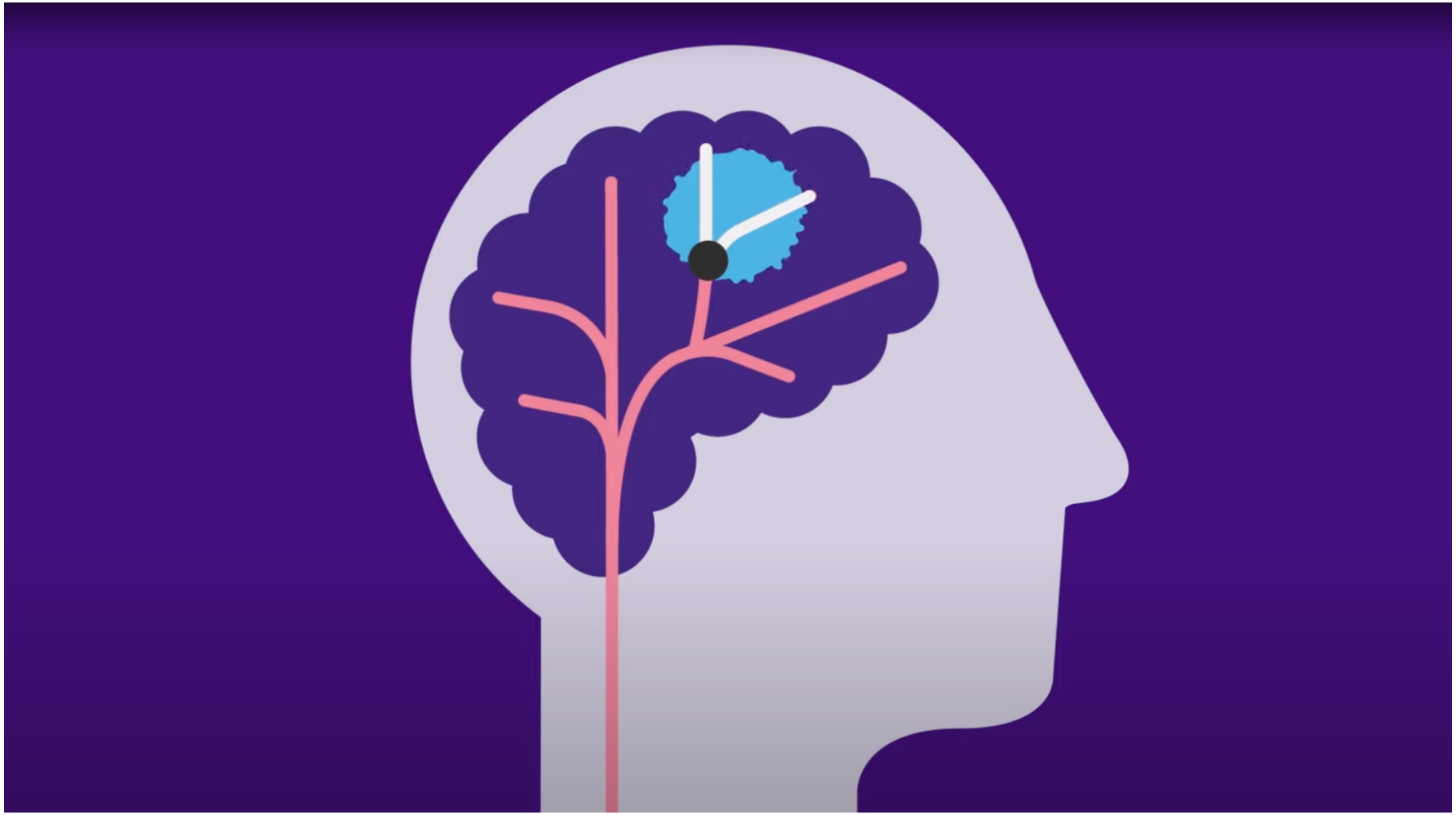
- Nathan James, PhD
- Elizabeth Lorenzi, PhD
- Scott Berry, PhD
- Roger Lewis, MD, PhD

STEP Design Committee

Especially:

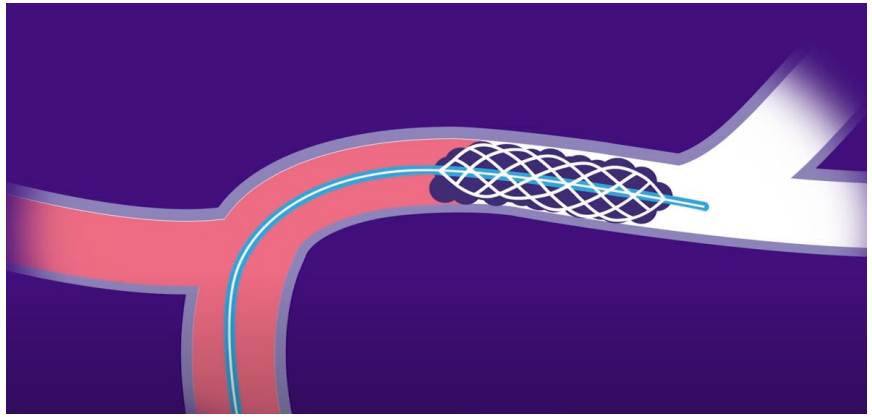
- Jordan Elm, PhD
- Jonathan Beall, PhD
- Byron Gajewski, PhD
- Eva Mistry, MD, MSc., FAHA
- Tudor Jovin, MD
- Pooja Khatri, MD, MSc.
- Jeffrey Saver, MD, FAHA, FAAN, FANA

Acute Ischemic Stroke



Stroke Association (2023). *What is thrombectomy?* [video]. https://www.stroke.org.uk/what-is-stroke/diagnosis-to-discharge/treatment/what-is-thrombectomy.

Endovascular Thrombectomy (EVT)



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Pivotal trials of EVT have established safety and efficacy of EVT in a relatively narrow range of baseline characteristics.

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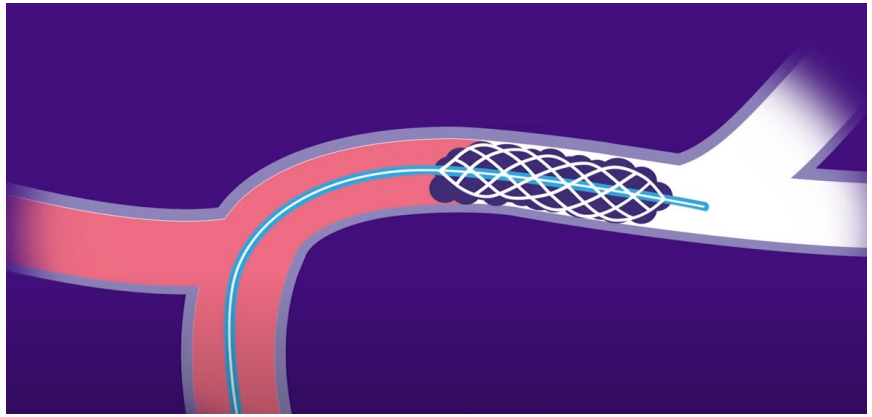

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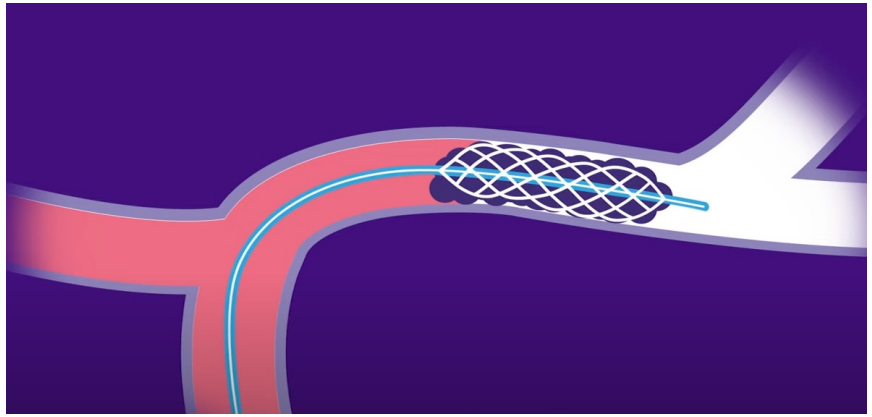
Initial EVT trials targeted patients with characteristics expected to maximize observed benefit.

It is probable that additional patients benefit from EVT.

Endovascular Thrombectomy (EVT)



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Pivotal trials of EVT have established safety and efficacy of EVT in a relatively narrow range of baseline characteristics.

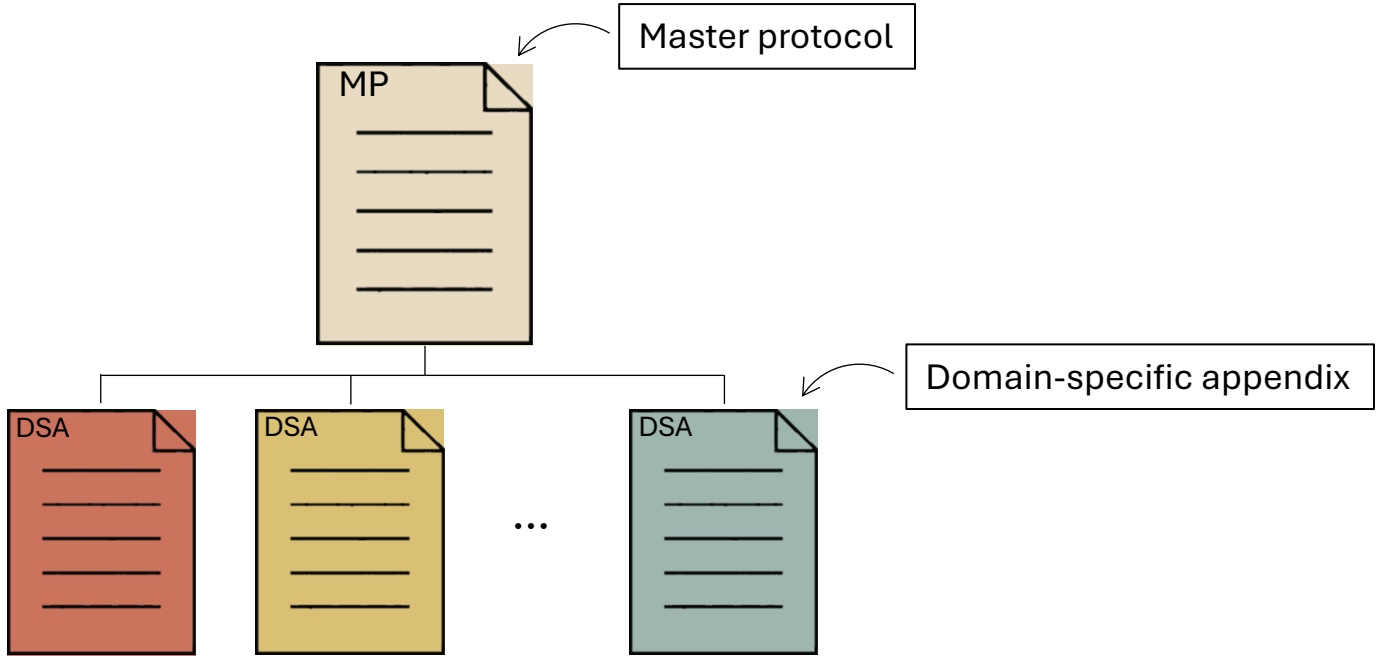
Initial EVT trials targeted patients with characteristics expected to maximize observed benefit.

It is probable that additional patients benefit from EVT.

Within the population where EVT is standard of care, there remain questions about how to maximize treatment benefit.

STEP

StokeNet Thrombectomy Endovascular Platform



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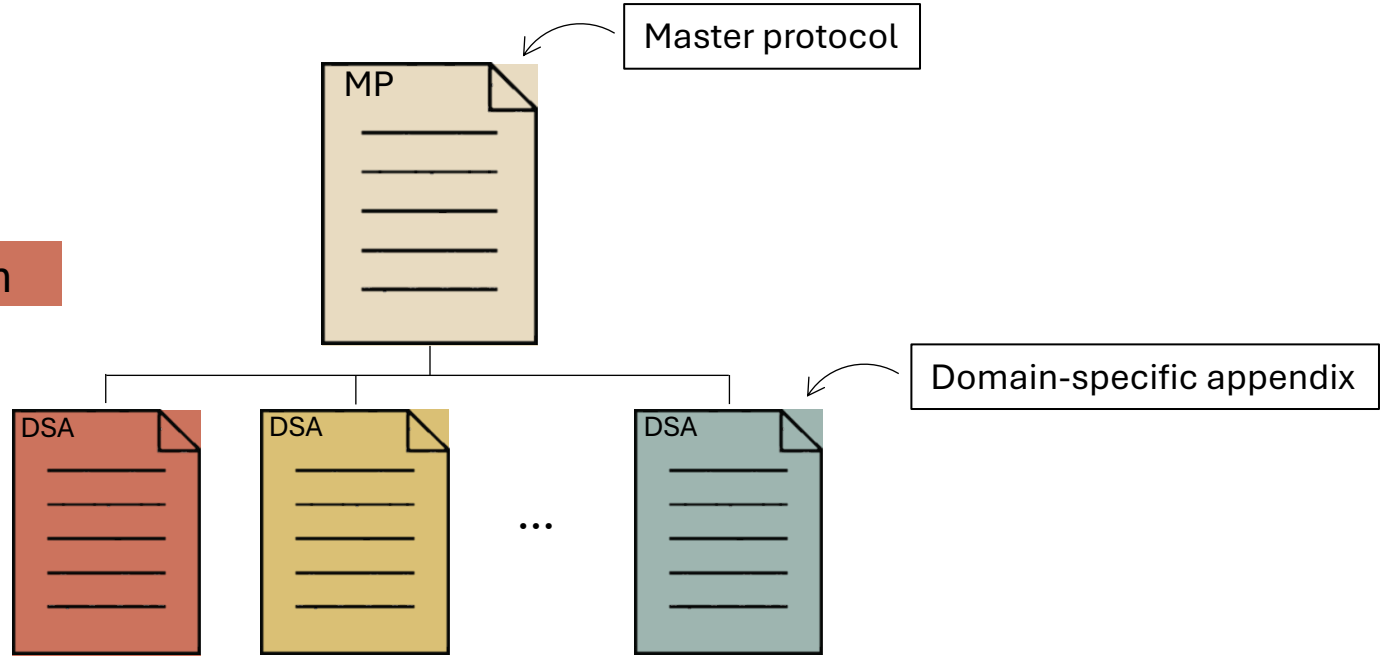
StokeNet Thrombectomy Endovascular Platform

Research Question: EVT Indication

Who should be treated with EVT?



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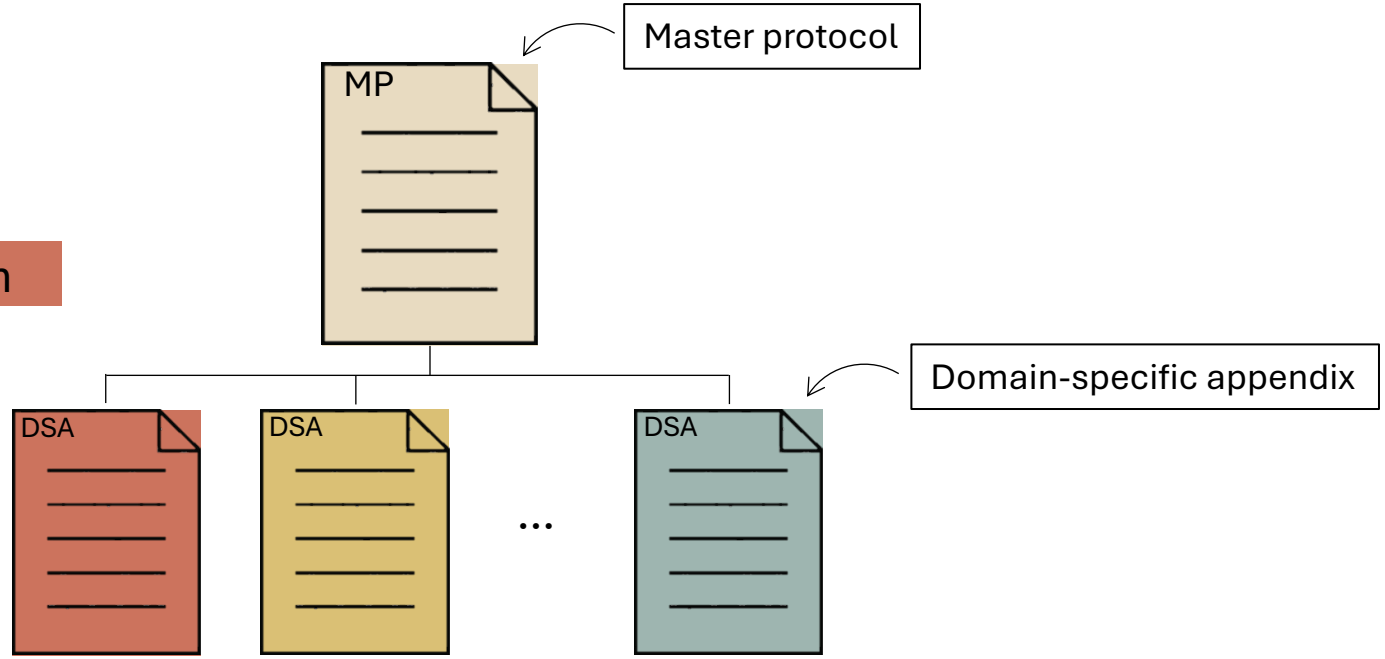
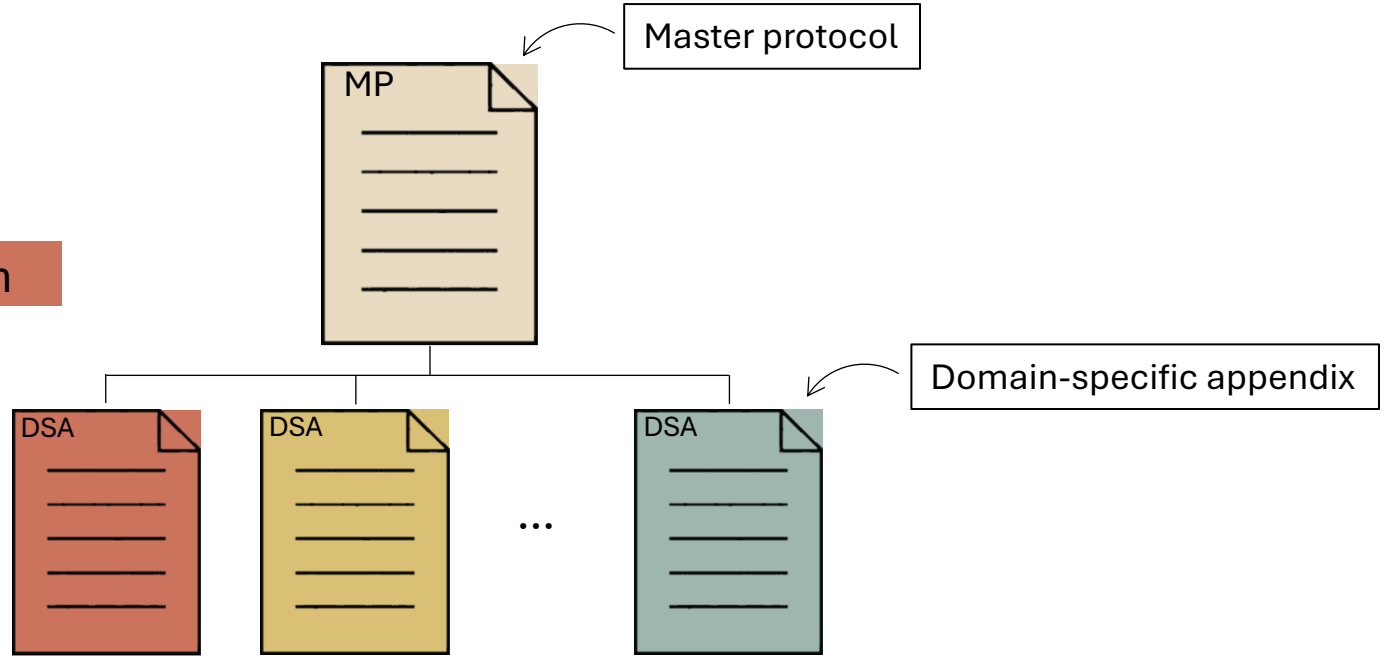


Research Question: Adjuvant Therapy

How to maximize patient benefit with EVT?

STEP

StokeNet Thrombectomy Endovascular Platform



Research Question: EVT Indication

Who should be treated with EVT?

Research Question: Adjuvant Therapy

How to maximize patient benefit with EVT?

Research Question: Technical Strategy

How to maximize patient benefit with EVT?

STEP

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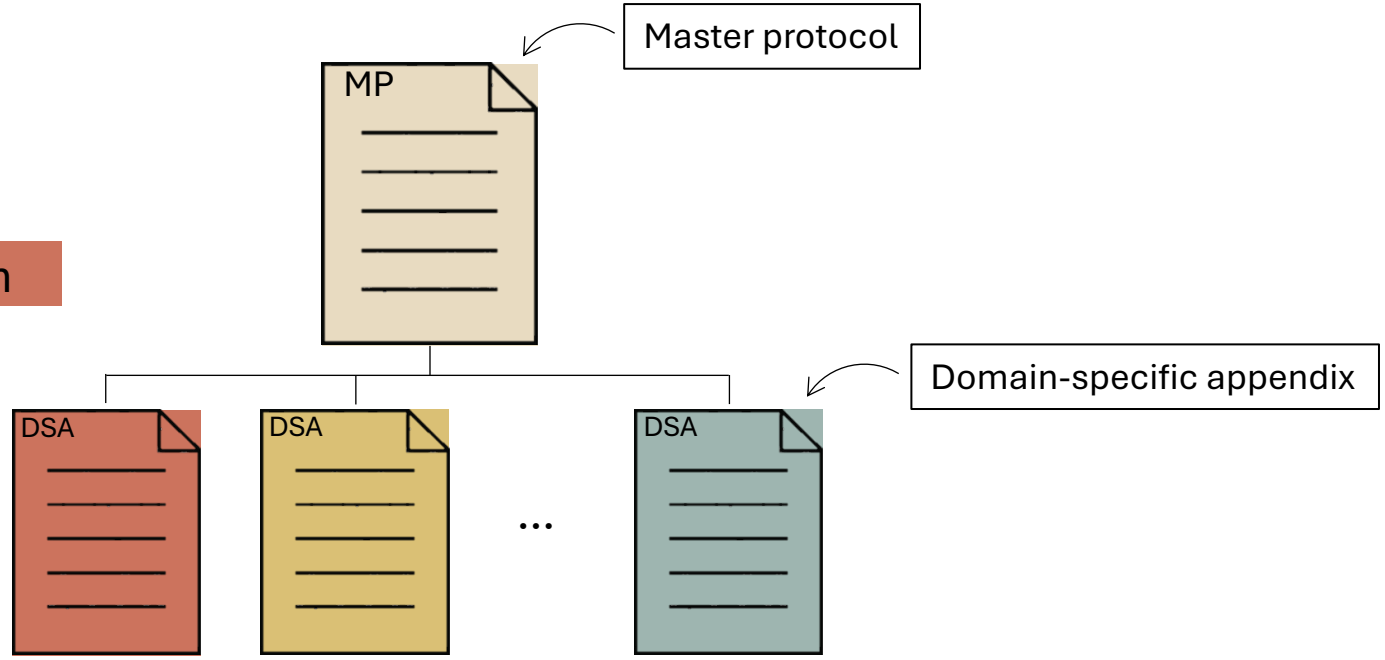


Research Question: EVT Indication

Who should be treated with EVT?

Research Question: Adjuvant Therapy

How to maximize patient benefit with EVT?

Research Question: Technical Strategy

How to maximize patient benefit with EVT?

Research Question: Combination strategies

Adjuvant therapy + technical strategy

Who should be treated with EVT?

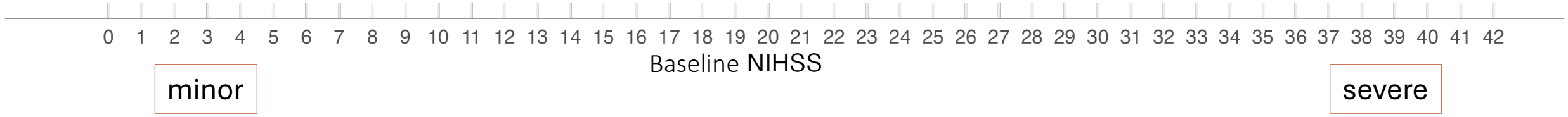
Medium vessel occlusions (MVO)

For a subset of patients who are not currently treated with EVT

- Medium vessel occlusions (MVO)
- Other inclusion criteria (time since last known well, etc.)

Baseline National Institutes of Health Stroke Scale (NIHSS)

- Measures neurological impairment caused by stroke
- Integer values from 0 to 42



Who should be treated with EVT?

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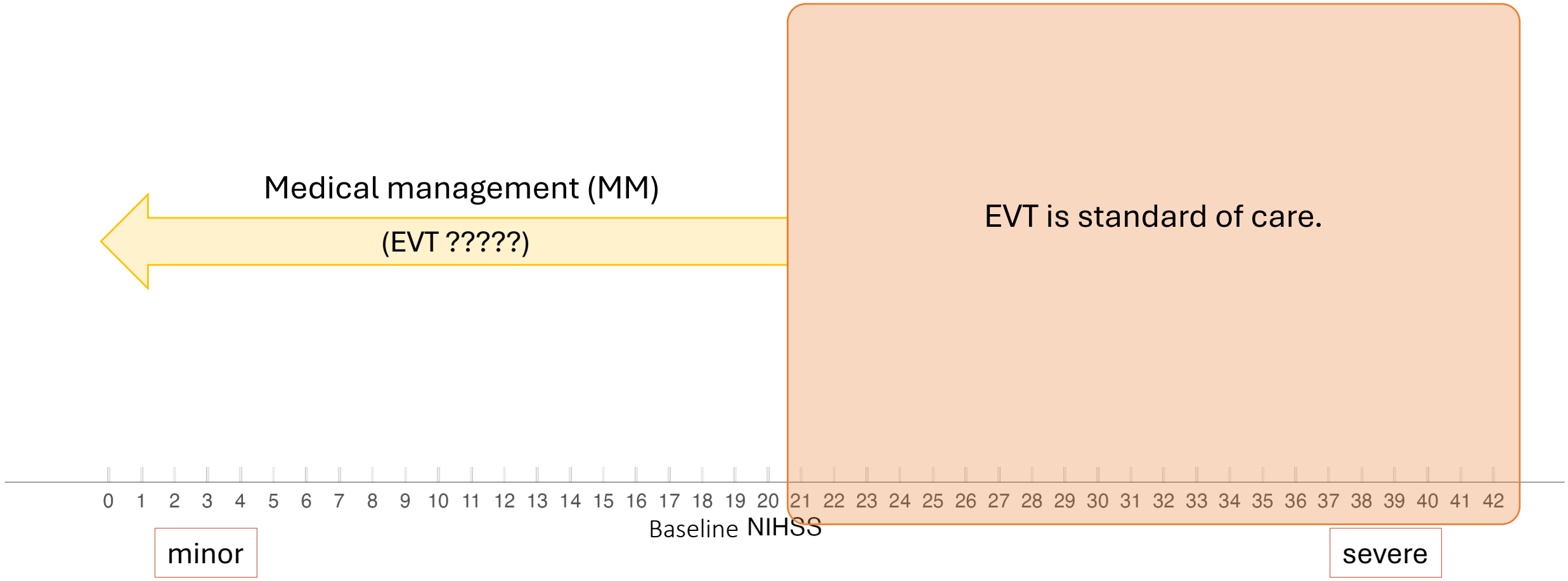

Who should be treated with EVT?

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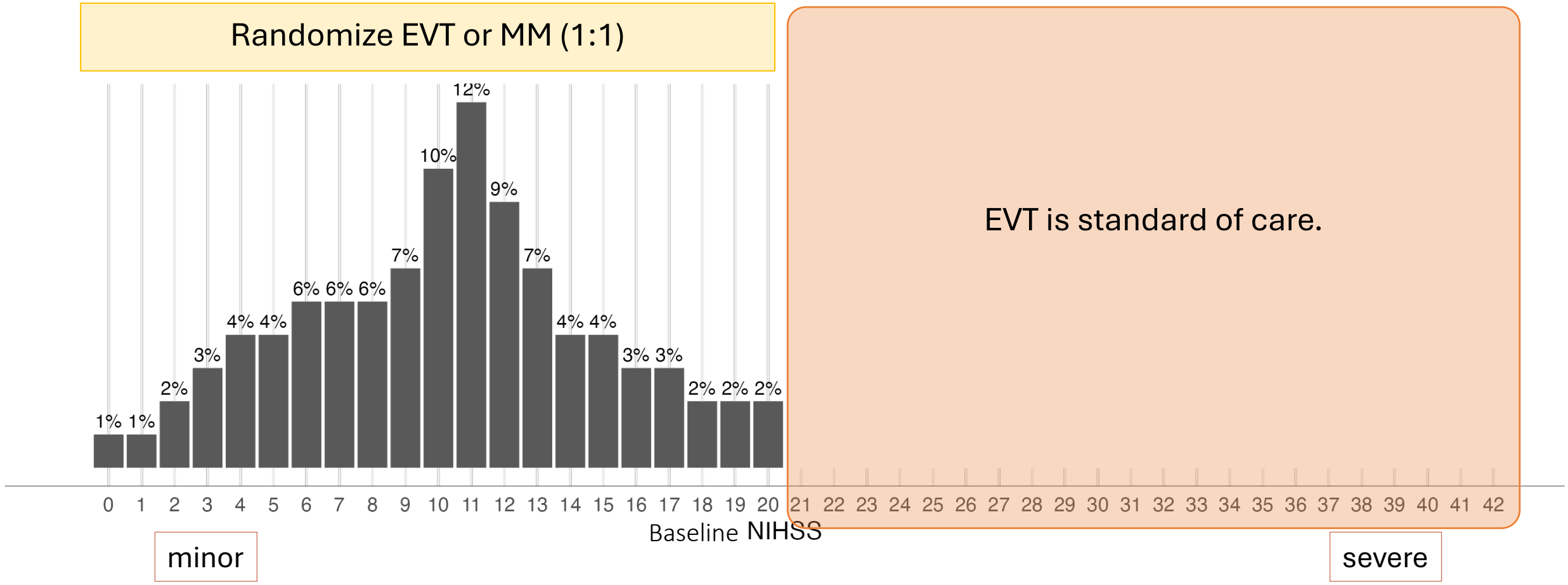
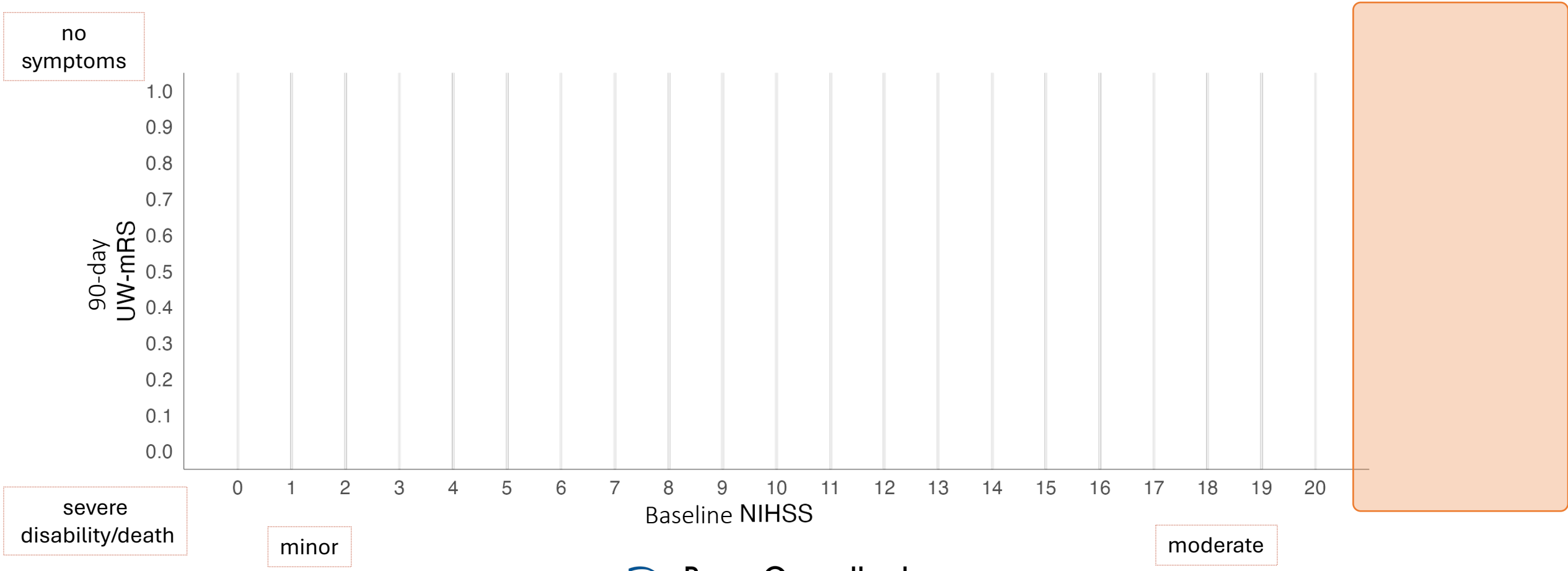


[Saber et. al. 2022]

Primary endpoint

90-day modified Rankin scale analyzed with utility weights [Chaisinanunkul et. al 2015]

- 90-day UW-mRS
- Measures functional outcome after stroke



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Bayesian Changepoint Model

Primary goals

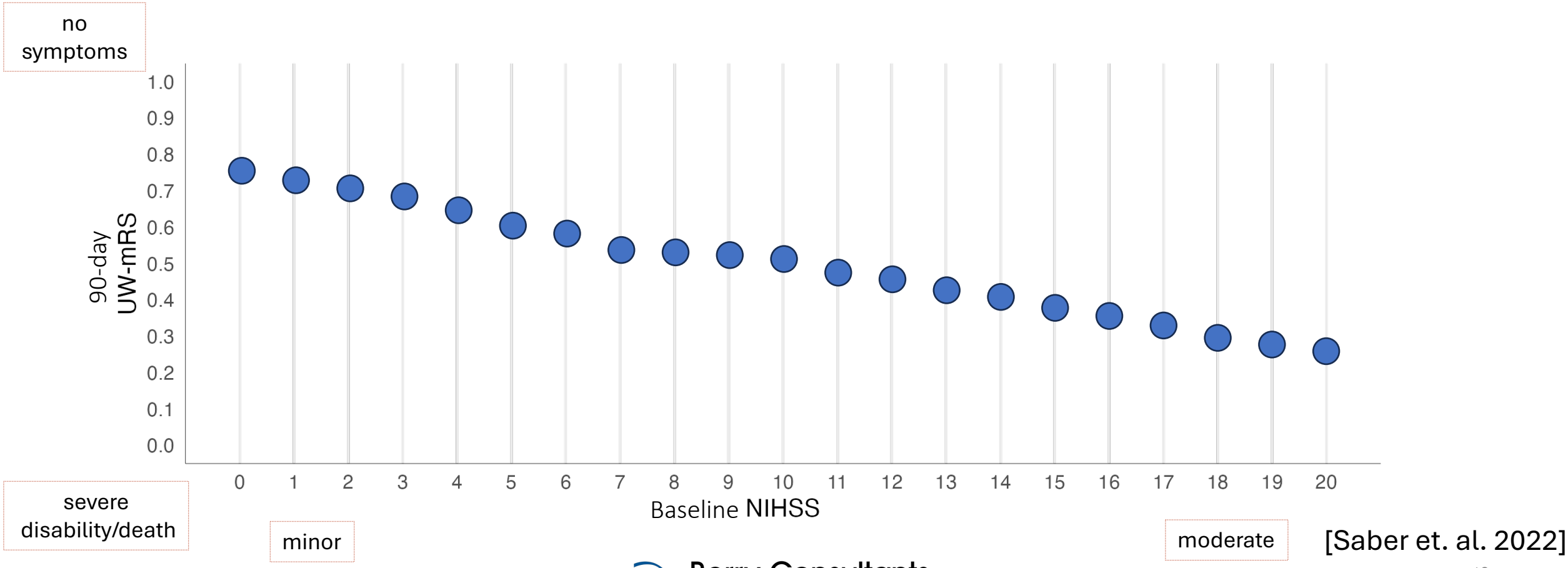
1. Estimation in each NIHSS
2. Monotonic decision-making
3. Identify where EVT is *no longer* superior to MM

Let $j = 0, \ldots, 20$ denote the NIHSS values.

Bayesian Changepoint Model

MM NDLM (β_j)

- Borrows from neighboring NIHSS for smooth estimation
- Intercepts

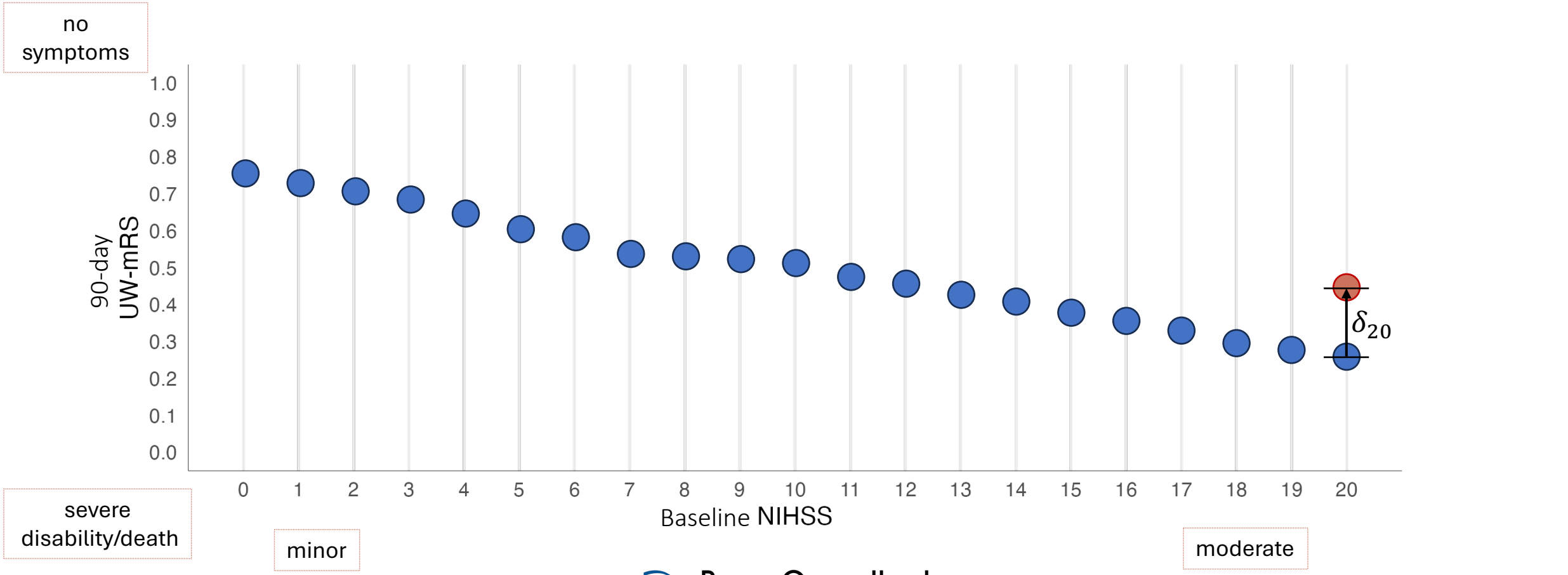


[Saber et. al. 2022]

Bayesian Changepoint Model

EVT difference (δ_j) from MM NDLM (β_j)

- Additive difference from MM for each NIHSS
- Treatment effects. Positive differences favor EVT. Negative differences favor MM.



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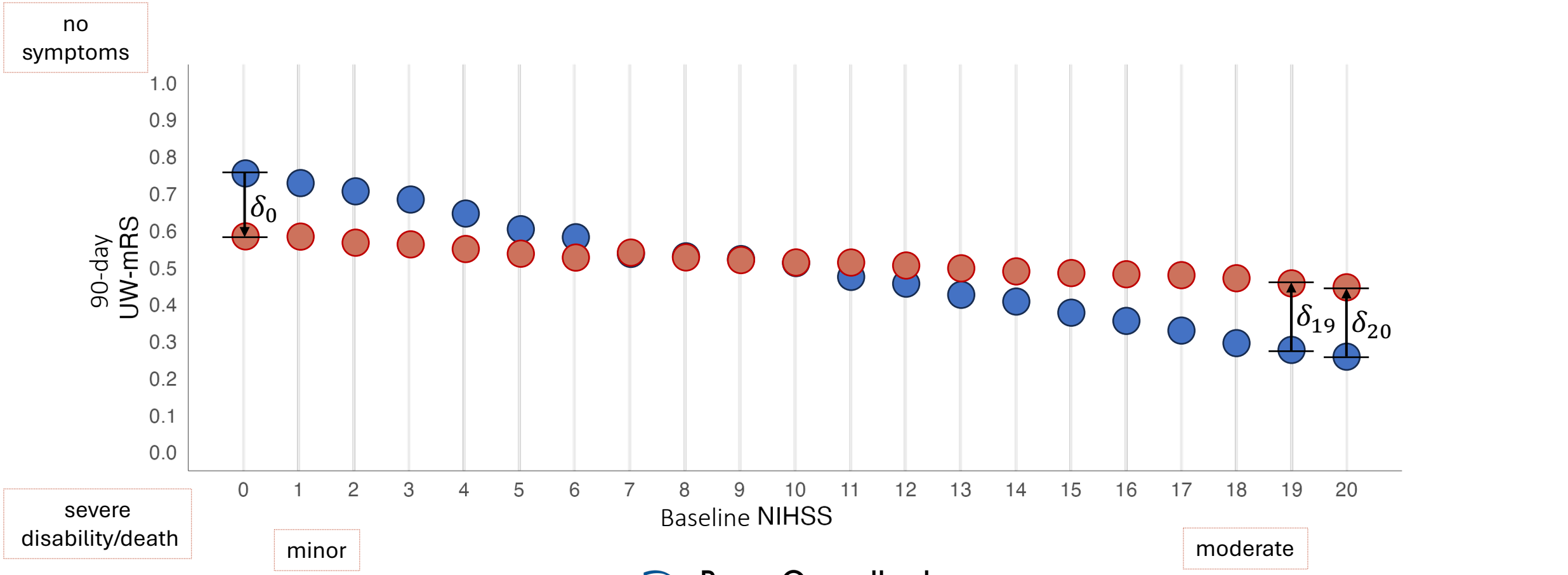

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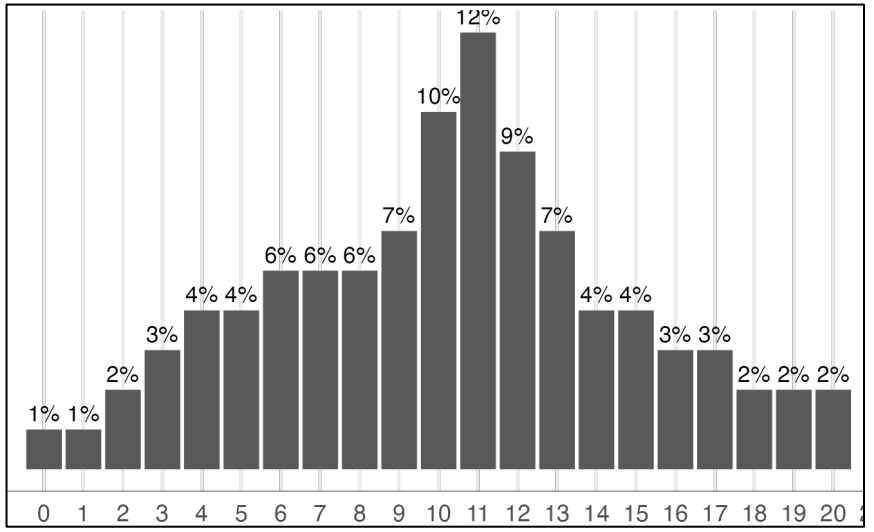
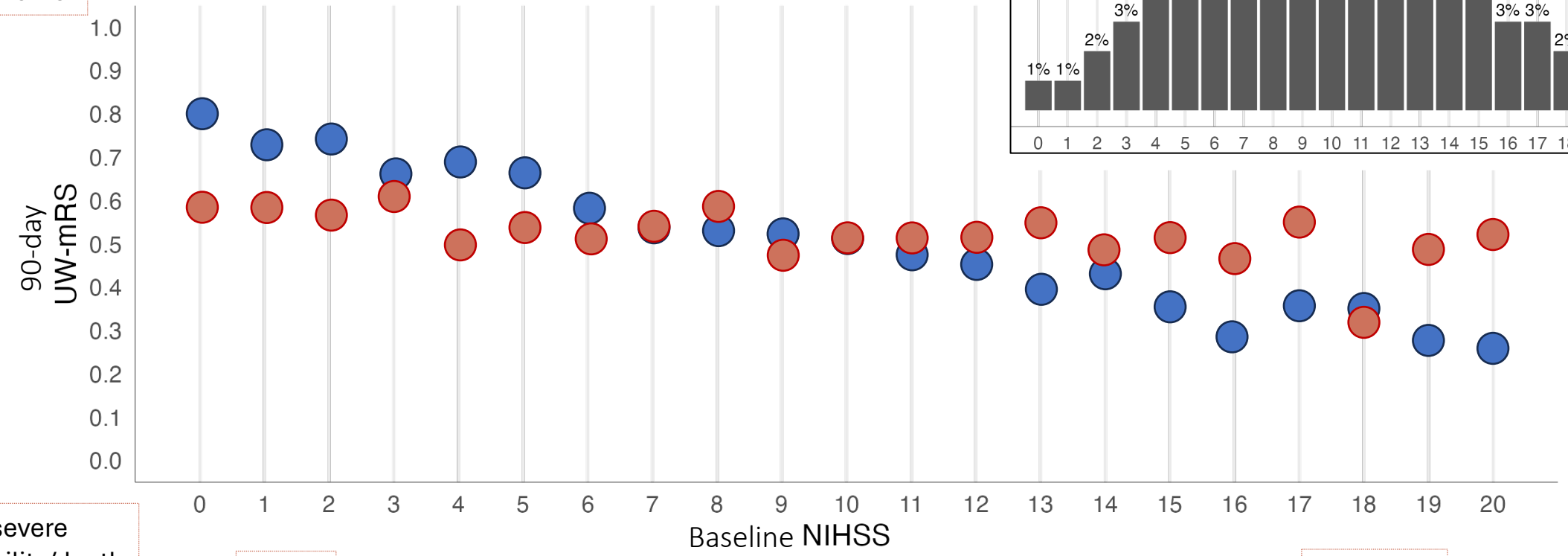
Bayesian Changepoint Model

EVT difference (δ_j) from MM NDLM (β_j)

- Monotonic decision process
- Add structure to the model to match biology

MM est. (β_j)
EVT est. ($\beta_j + \delta_j$)





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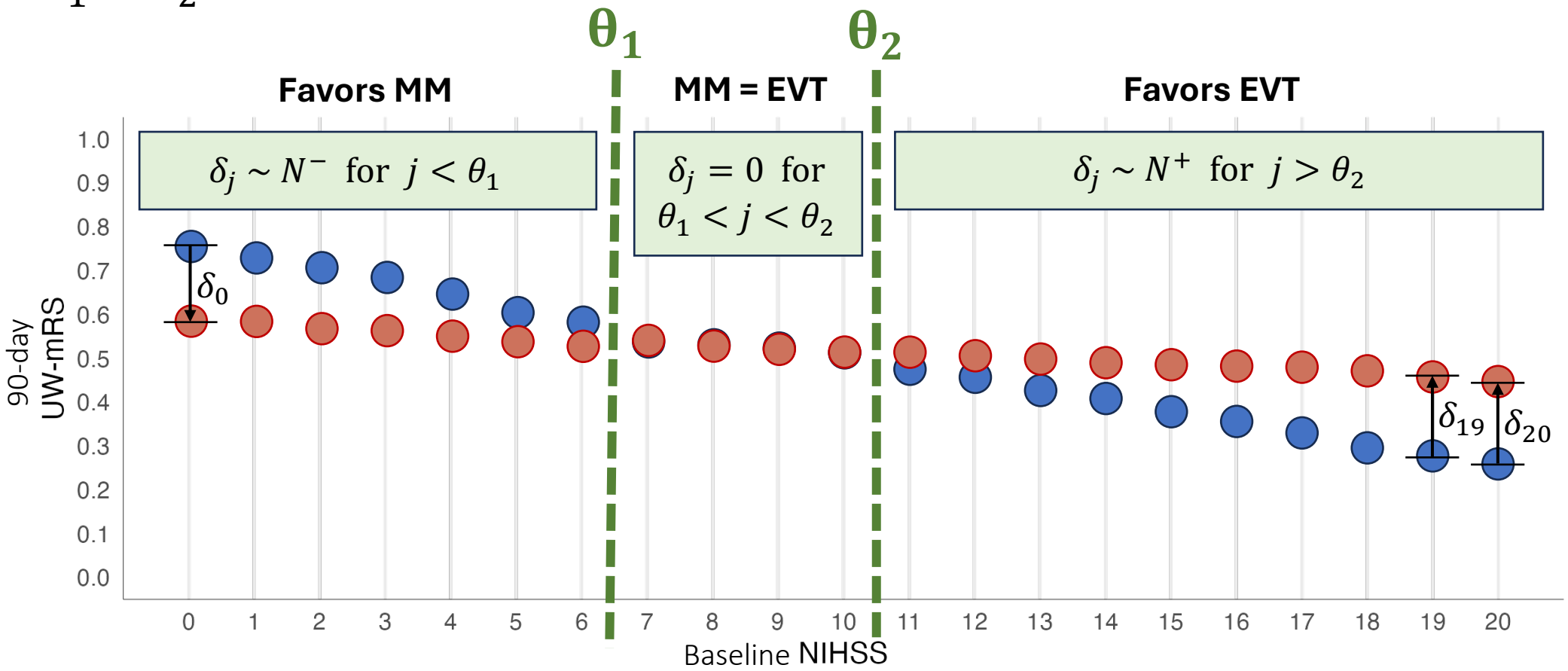
Bayesian Changepoint Model

EVT difference (δ_j) from MM NDLM (β_j)

- δ_j support restricted by changepoint (θ_1, θ_2) locations
- $\theta_1 \leq \theta_2$



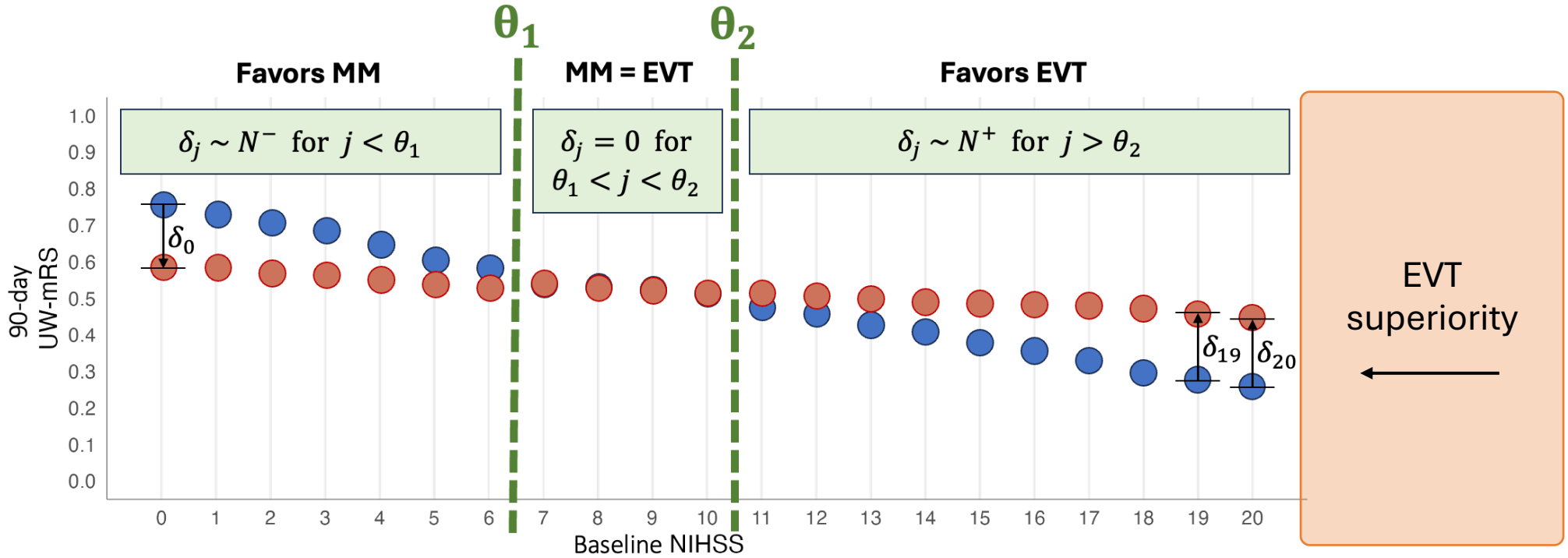
Who should be treated with EVT?

θ_2 directly answers the scientific question

MM est. (β_j)
EVT est. (β_j + δ_j)

<u>EVT superiority</u> in NIHSS bin *j* if

- $\Pr(j > \theta_2) > 0.96$
- $\Pr(\delta_j > 0) > 0.96$



Prior belief

NIHSS (j)

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0.16	0.19	0.23	0.26	0.30	0.33	0.36	0.40	0.43	0.47	0.50	0.53	0.57	0.60	0.64	0.67	0.70	0.74	0.77	0.81	0.84

Prior probability EVT superior to MM ($j > \theta_2$ or $\delta_j > 0$)

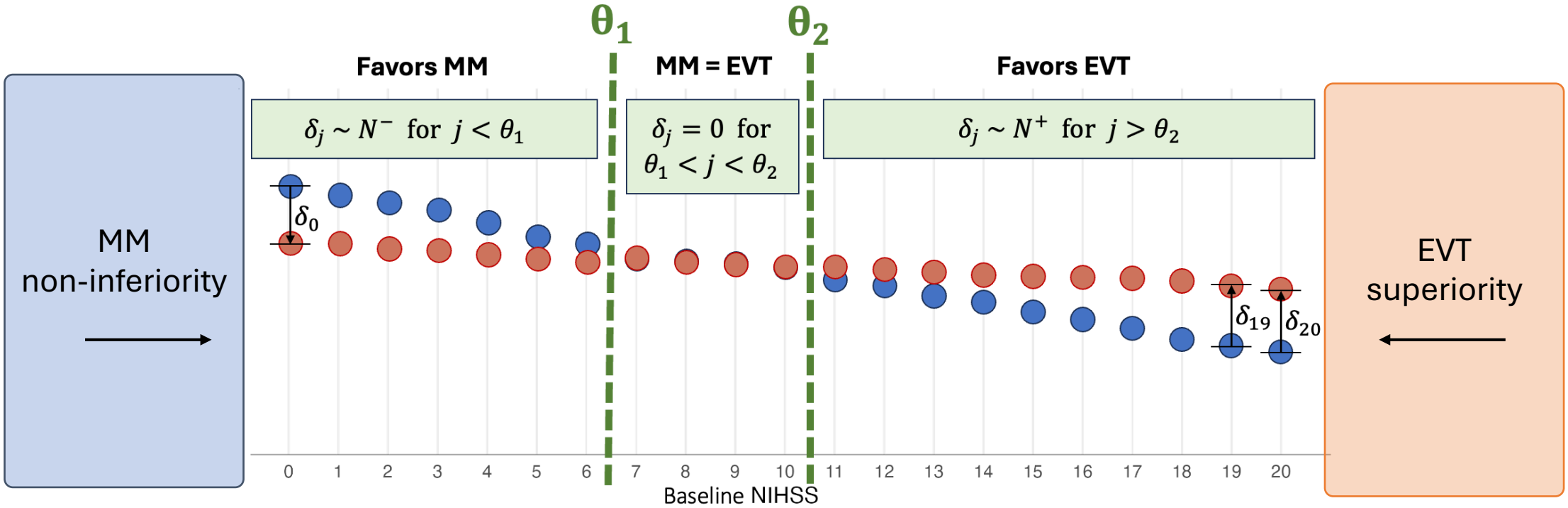
Who should NOT be treated with EVT?

θ_2 directly answers the scientific question

MM est. (β_j)
EVT est. (β_j + δ_j)

MM non-inferiority in NIHSS bin *j* if

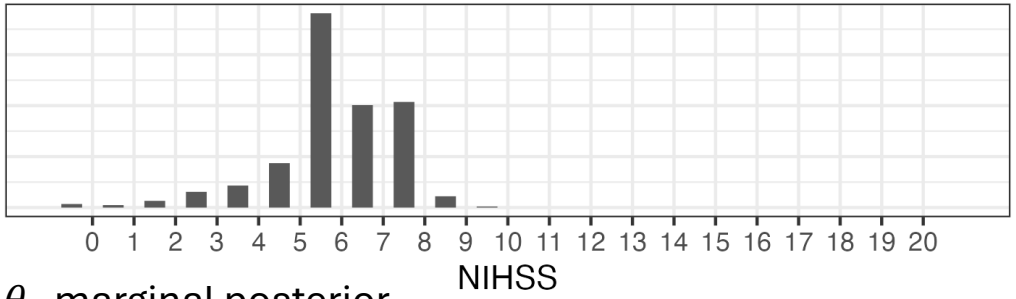
- $\Pr(j < \theta_2) > 0.96$
- $\Pr(\delta_j \leq 0) > 0.96$



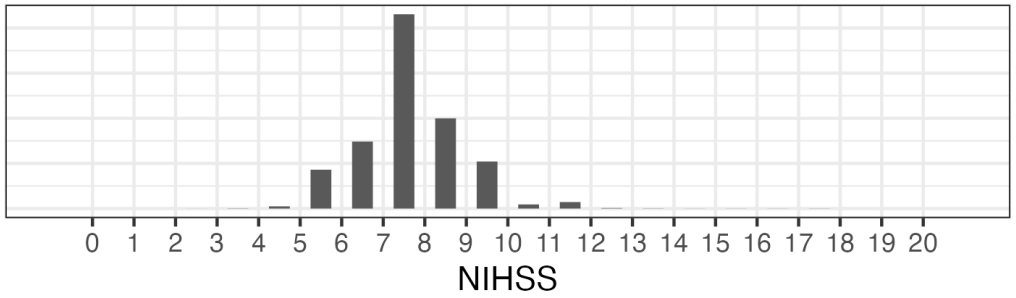
Example Trial

N = 1000

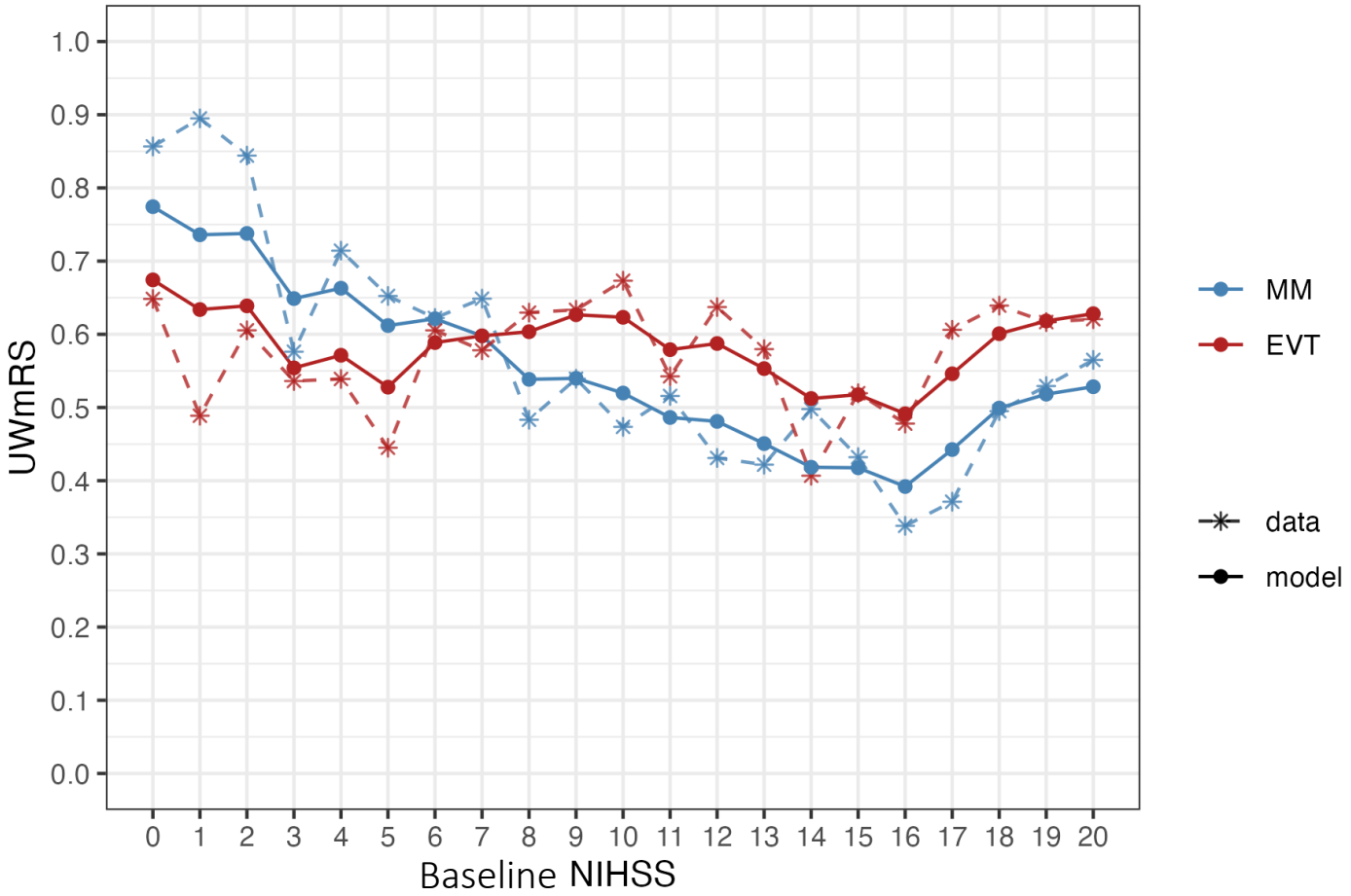
θ_1 marginal posterior



θ_2 marginal posterior



Data means and model estimates



NIHSS	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
EVT superior to MM	0	0	0	0	0	0.01	0.09	0.24	0.67	0.87	0.97	0.98	1	1	1	1	1	1	1	1	1
MM non-inferior to EVT	1	1	1	1	1	0.99	0.91	0.76	0.33	0.13	0.03	0.02	0	0	0	0	0	0	0	0	0

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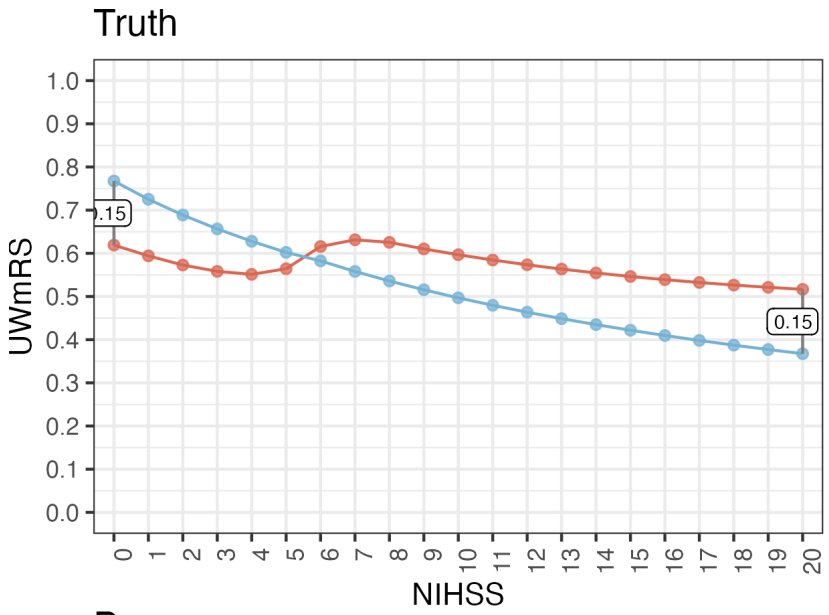
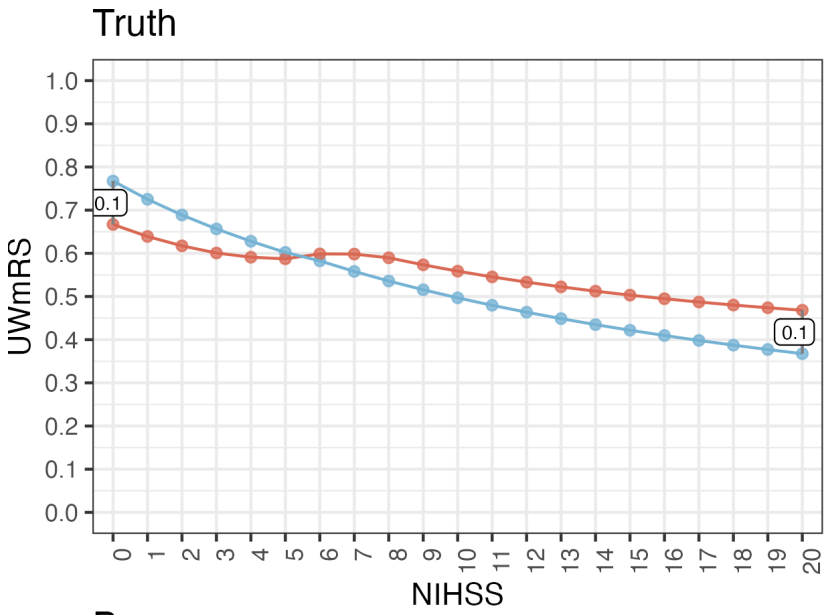
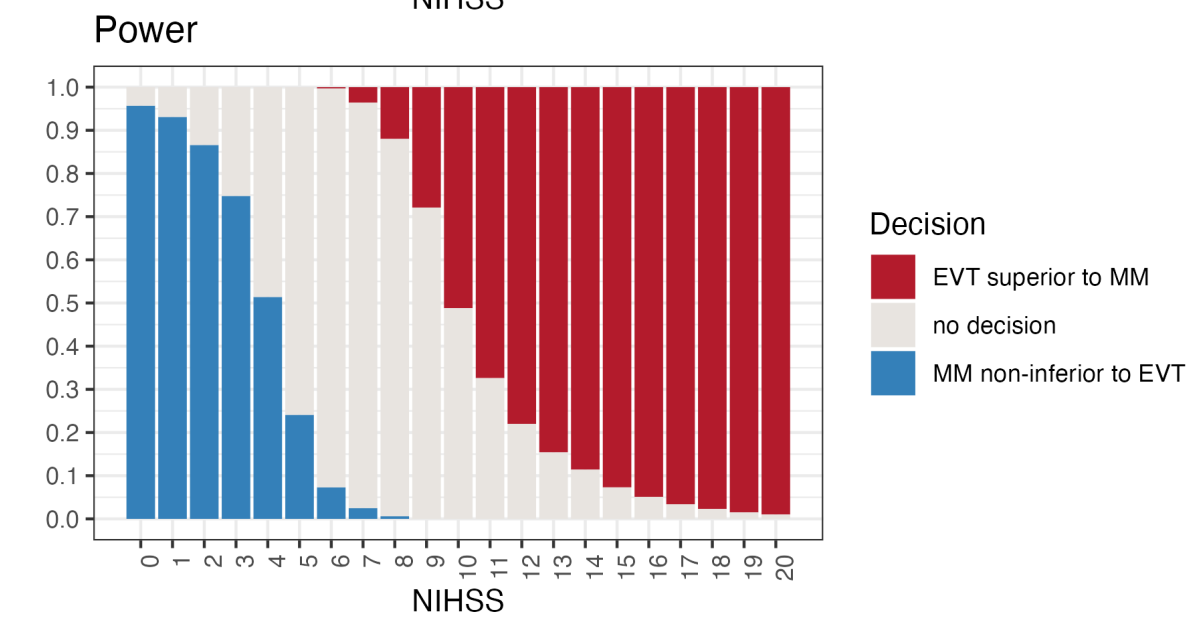
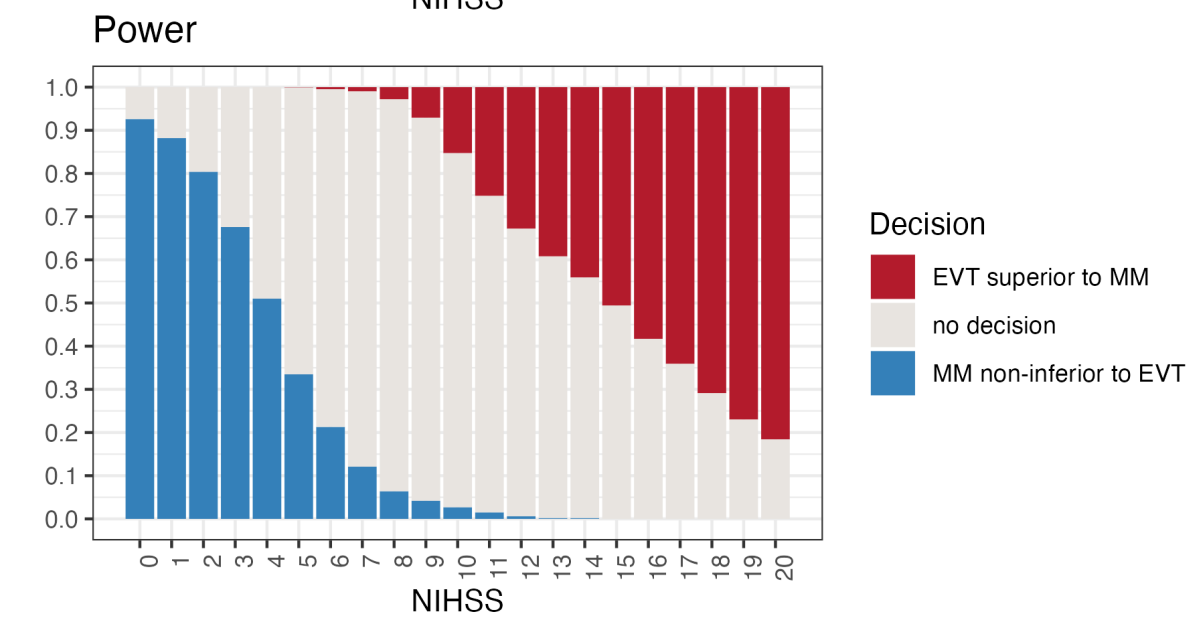
Operating Characteristics









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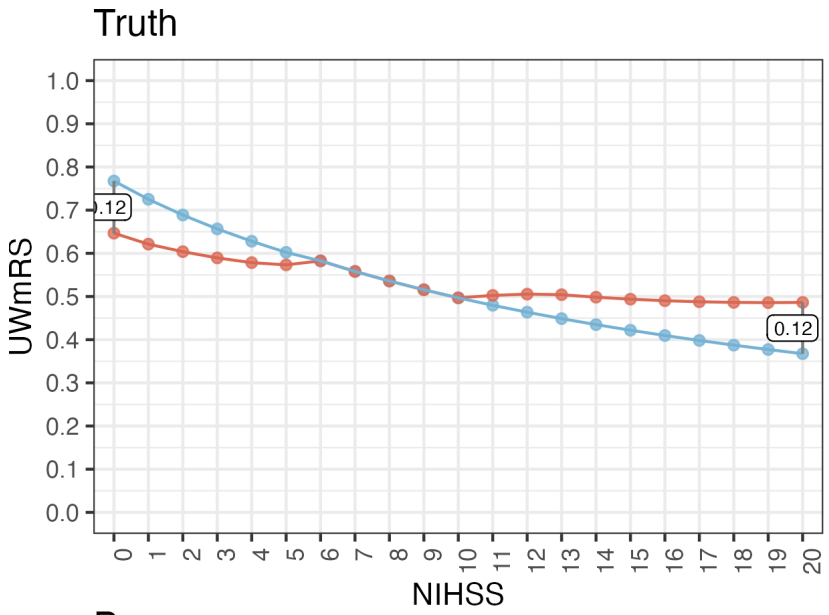

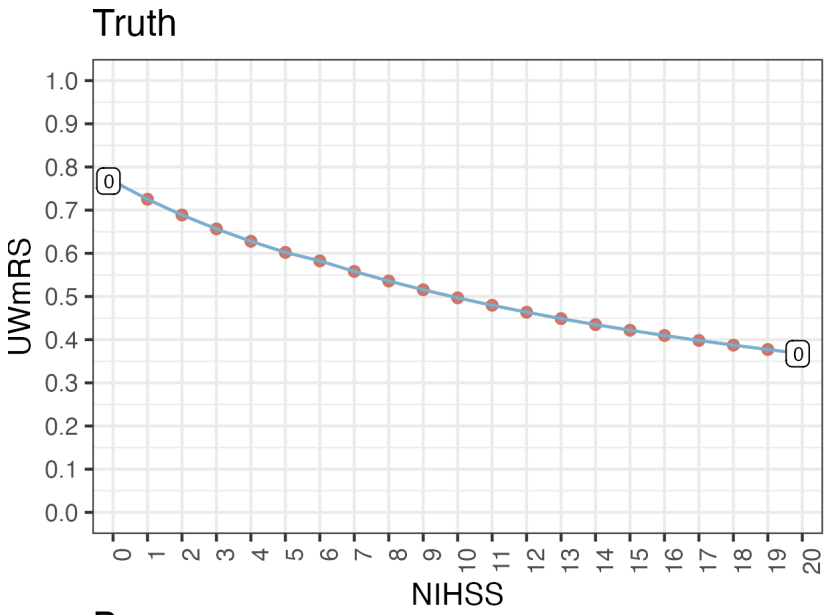

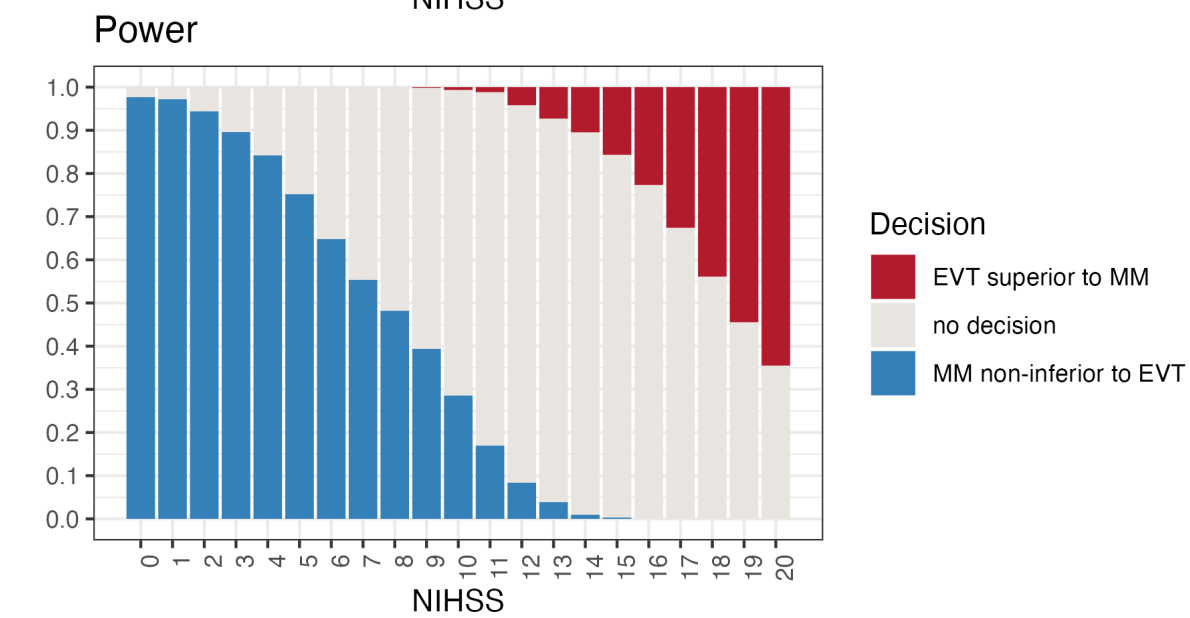

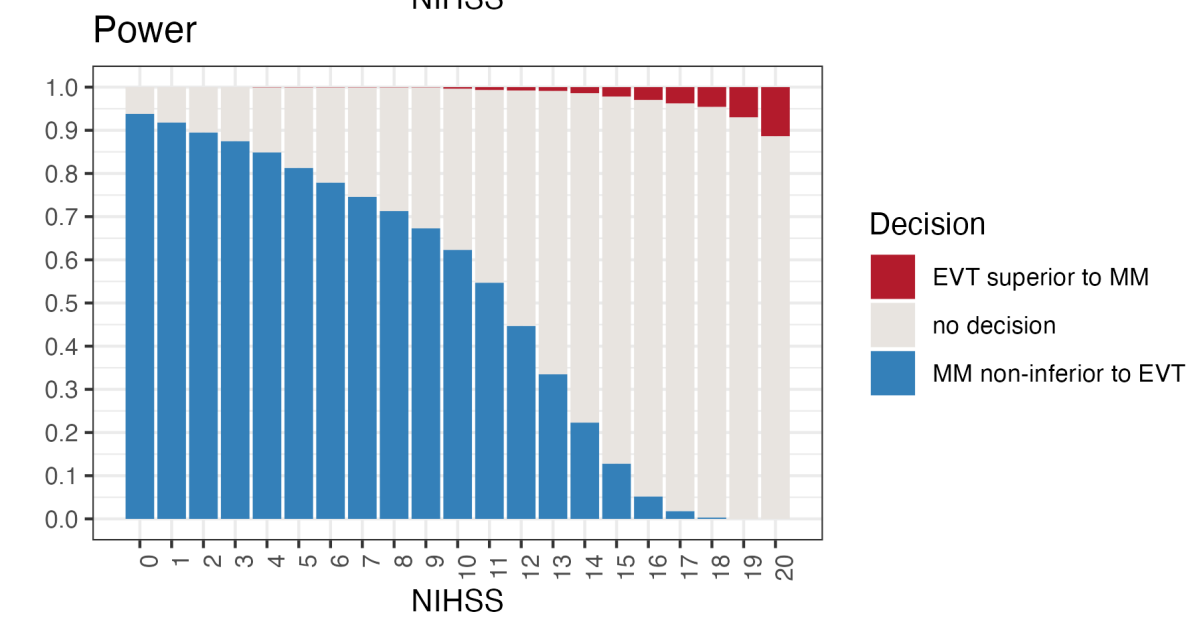

Summary

I've made a number of simplifications for this presentation.

In the trial:

- MVO: MVO1 & MVO2 vessel classes
  - Borrowing in the MM NDLMs and θ_2 locations
- Large vessel occlusions (LVO)
- Frequently scheduled interim analyses

Take away:

Pre-specification of a flexible model to directly answer the scientific question.

Thank you!

Amy Crawford, PhD
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