What is the Current Role of EPD in TAVI?

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Disclosures

Grant Support/Drugs

– MyoKardia/BMS

Grant Support/Devices

– Edwards Lifesciences
- Abbott Vascular
– Boston Scientific
- CathWorks
– Corvia
- Phillips
– I-Rhythm
- Zoll/Therox

Consulting/Advisory Boards

– Medtronic
- Edwards Lifesciences
– Boston Scientific
- Abbott Vascular
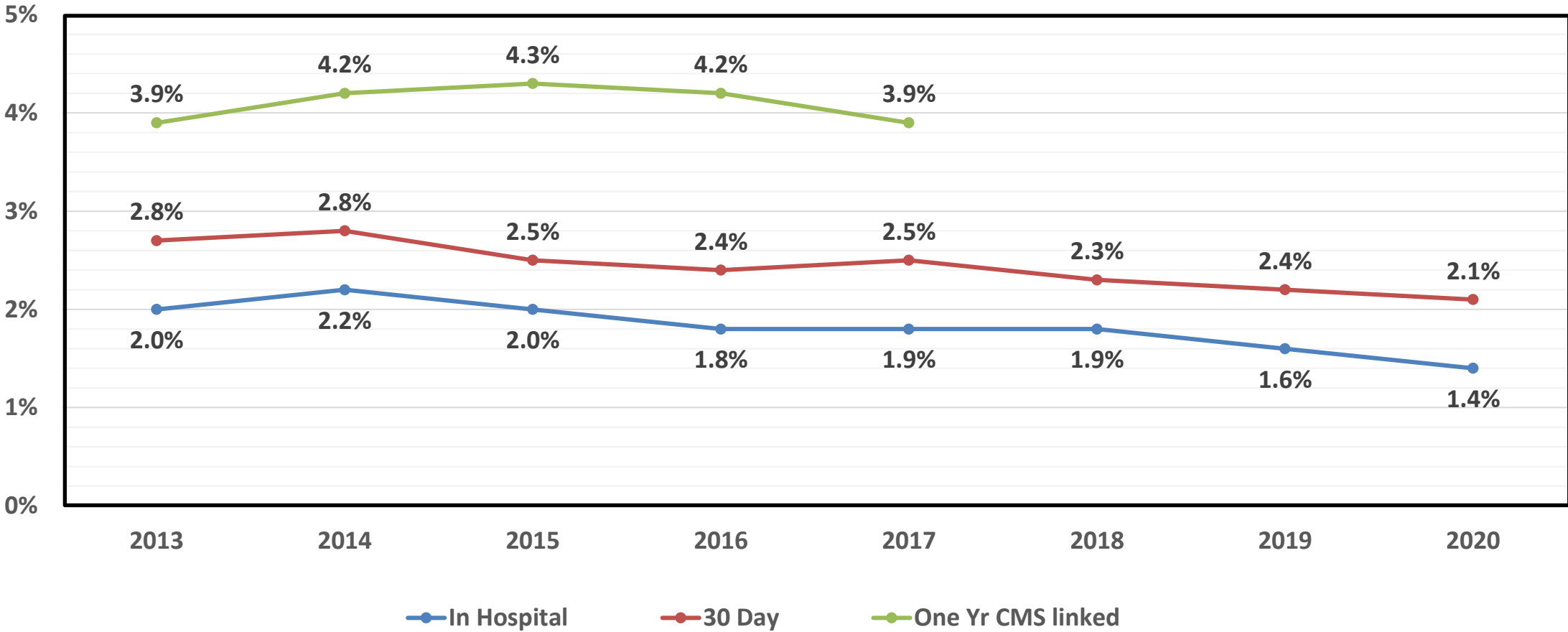– Corvia
- Impulse Dynamics

Embolic Protection for TAVR

- Is TAVR-related stroke really a problem?

- What is the benefit of EPD in current practice?

- Can we select appropriate patients?

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TVT Registry: TAVR-Related Stroke

Line chart showing TAVR-related stroke rates from 2013 to 2020 for three measures:

One Yr CMS linked: 2013: 3.9%, 2014: 4.2%, 2015: 4.3%, 2016: 4.2%, 2017: 3.9%

30 Day: 2013: 2.8%, 2014: 2.8%, 2015: 2.5%, 2016: 2.4%, 2017: 2.5%, 2018: 2.3%, 2019: 2.4%, 2020: 2.1%

In Hospital: 2013: 2.0%, 2014: 2.2%, 2015: 2.0%, 2016: 1.8%, 2017: 1.9%, 2018: 1.9%, 2019: 1.6%, 2020: 1.4%

Legend: In Hospital — 30 Day — One Yr CMS linked

Impact of Stroke on Clinical and Economic Outcomes

Outcome	Adjusted HR or Diff. (95% CI)
Death	
30-day	3.2 (2.9 to 3.5)
1-year	1.5 (1.4 to 1.6)
5-year	1.2 (1.1 to 1.2)
Days at home	-16 (-18 to -14)
1-year cost	$9245 ($7665 to $10,825)

- Analysis of 129,000 TAVR procedures from Medicare Claims (2012-17)

- In-hospital stroke occurred in 4.3%

- Associated with increased risk of mortality (through 5 yrs) and ~$9000 increase in 1-year costs
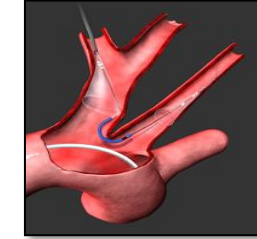
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Current Cerebroembolic Protection Devices

Device	Access	Sheath Size	Approval Status
Sentinel	Right radial	6F	FDA Approved CE Mark
TriGuard 3	Femoral	8F	CE Mark
ProEmbo	Left radial	6F	Investigational
Emblok	Femoral	12F	Investigational
Emboliner	Femoral	9F	Investigational
Point-Guard	Femoral	10F	Investigational

SENTINEL IDE Trial

Protected New Volumes, mm^3

p = 0.33
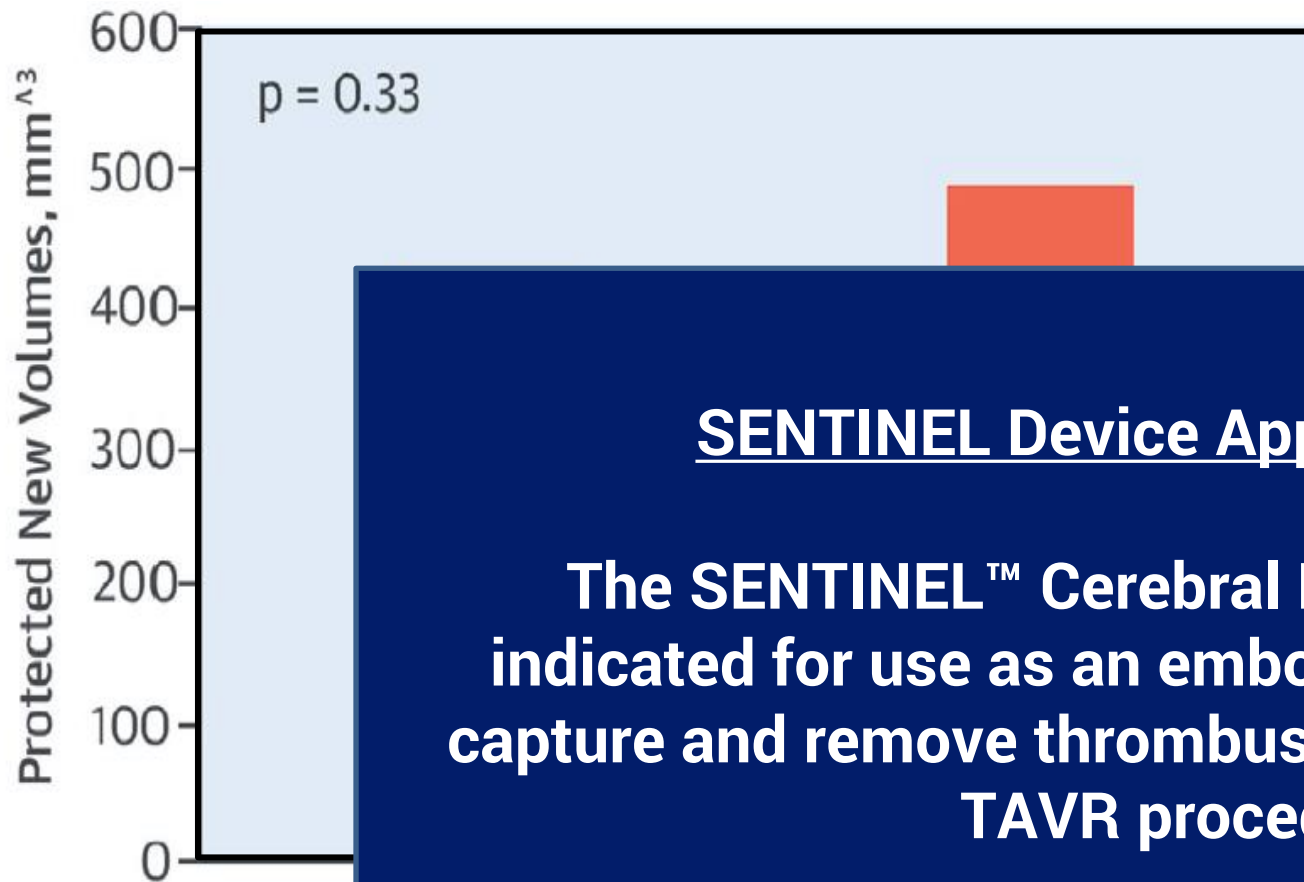
- **Design:** 363 high-risk TAVR patients randomized to Sentinel or no Sentinel

...duction
...n
...s on MRI

SENTINEL Device Approval Language

The SENTINEL™ Cerebral Protection System is indicated for use as an embolic protection device to capture and remove thrombus/debris while performing TAVR procedures.[1]
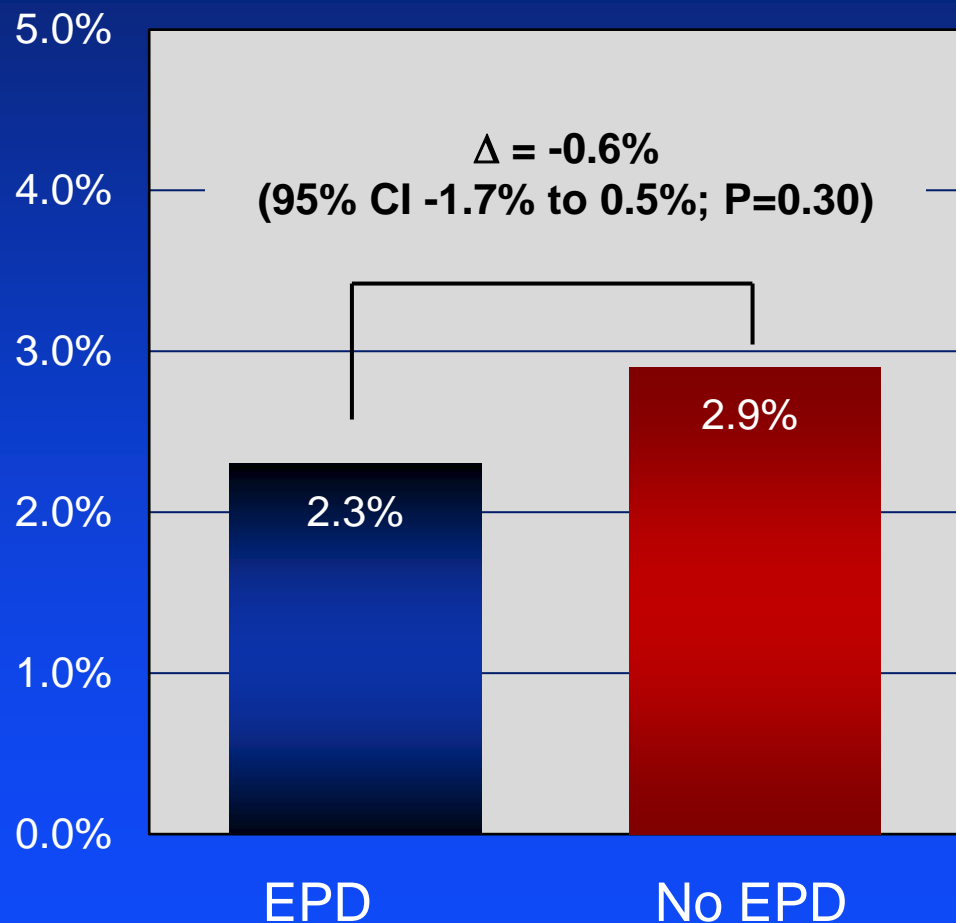
...2% (p=0.05)
...p=0.25)

Kapadia et al. JACC 2017; 69: 367-77

PROTECTED TAVR Trial Design

Patients undergoing commercial TF TAVR*, N=3000
- **Patients of all risk categories eligible**

Neurological exam pre-procedure

1:1

TAVR without CEP
N=1500

TAVR with Sentinel
N=1500

Neurological exam in all patients post-procedure

Primary endpoint: Stroke at 72h or Discharge

Kapadia SR, et al. N Engl J Med 2022; 387:1253-1263
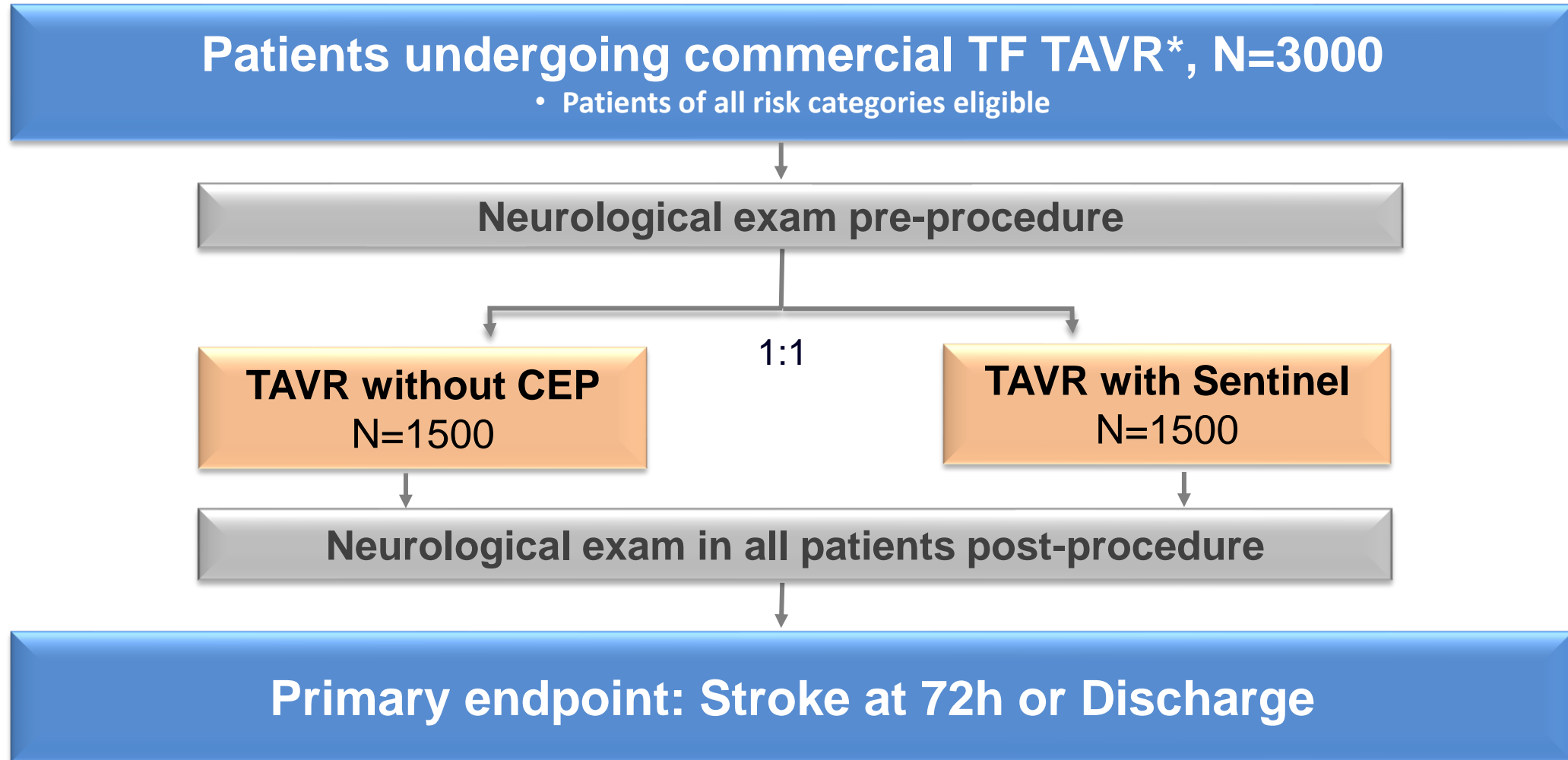
PROTECTED TAVR: Results

Primary Endpoint: Stroke at 72 hrs

Δ = -0.6%
(95% CI -1.7% to 0.5%; P=0.30)

EPD: 2.3%
No EPD: 2.9%

Prespecified Secondary Endpoints

	EPD	No EPD	P-Value
Disabling Stroke	0.5%	1.3%	0.02
Non-Disabling Stroke	1.7%	1.5%	NS
TIA	0.1%	0.1%	NS
Stroke, TIA, or Delirium	3.1%	3.7%	NS
Death	0.5%	0.3%	NS
AKI	0.5%	0.5%	NS

Sentinel: Updated Meta-Analysis– Any Stroke

	EPD		No EPD		Weight	RR (95% CI)
MISTRAL-C	0	32	2	33	1.5%	0.21 [0.01, 4.13]
CLEAN-TAVI	4	50	4	50	7.7%	1.00 [0.26, 3.78]
SENTINEL	13	231	10	110	21.7%	0.62 [0.28, 1.37]
PROTECTED TAVR	34	1501	43	1499	69.1%	0.79 [0.51, 1.23]
Total	**51**	**1814**	**59**	**1692**		**0.75 [0.52, 1.08]**
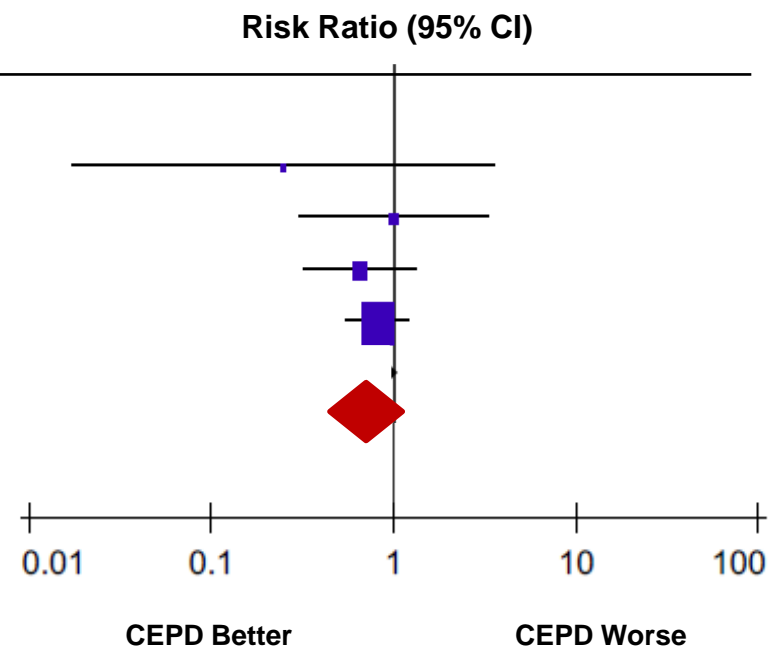
Could we have predicted PROTECTED-TAVR?

Relative Risk of Stroke (EPD vs. no EPD)

Butala NM, et al. Circulation 2021; 143:2229–2240
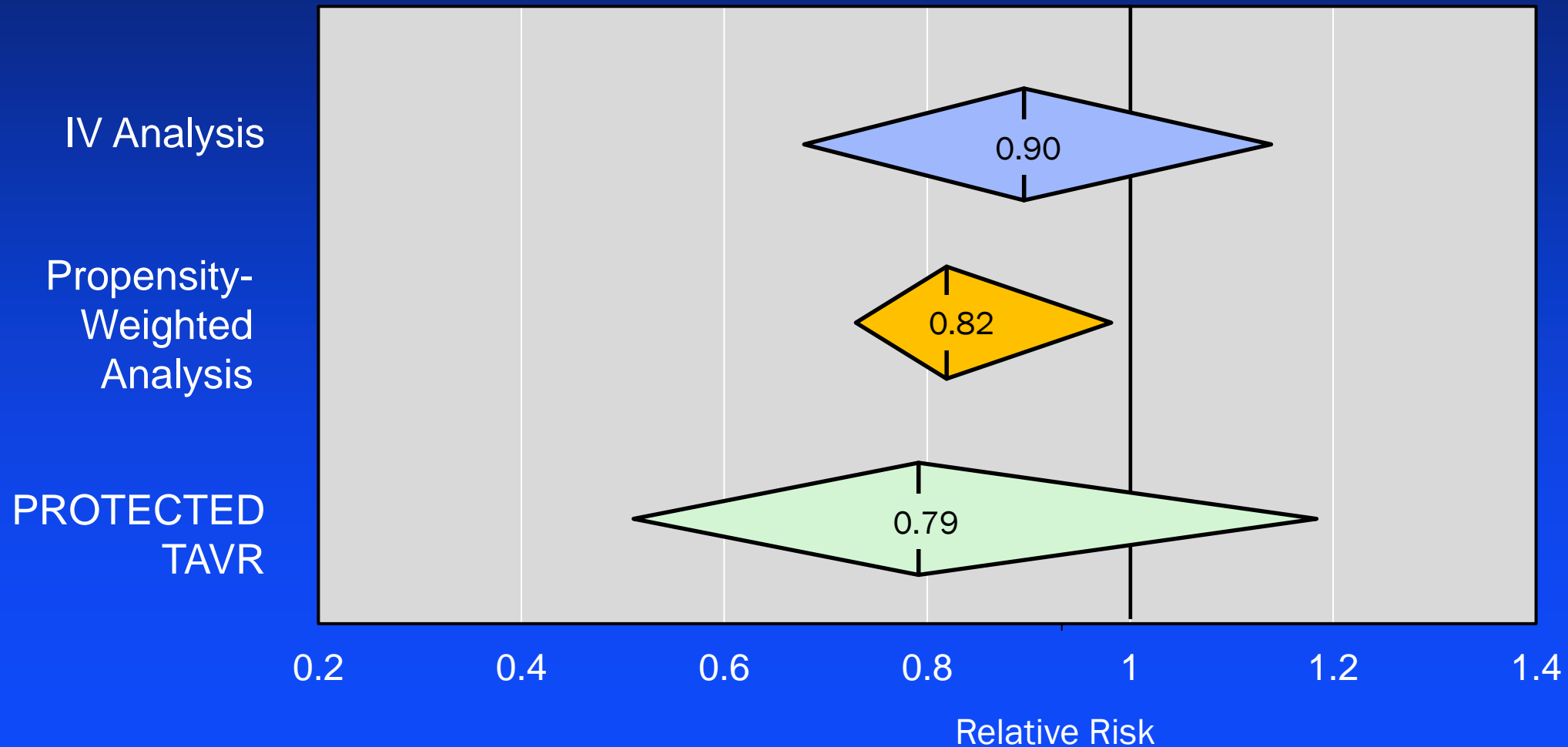
What about the disabling stroke data?

- No question that disabling stroke is the endpoint our patients and their families are most concerned about

- In light of previous studies, suggestion that EPD converts major strokes into minor strokes is mechanistically and biologically plausible

- However, in the context of an overall neutral trial, results for a secondary outcome (among 6 assessed) should be considered hypothesis-generating and require confirmation

  - *Absolute risk reduction may be as low as 0.1%, even <u>before</u> accounting for multiple comparisons*

"95% confidence intervals for secondary endpoints should not be used to infer definitive treatment effects"

- Kapadia S, et al. <u>NEJM</u> 9/17/22

Summary: Benefits of Sentinel in TAVR

Definitely…

- Captures debris en route to brain (3/3 trials)

Possibly…

- Reduction in CNS lesion volume in protected territories (1/3 trials positive)

Unproven…

- Reduction in stroke (0/4 trials positive); meta-analyses neutral; large observational studies (n=4) all negative except one that did the analysis wrong

- Improved late neurocognitive outcomes

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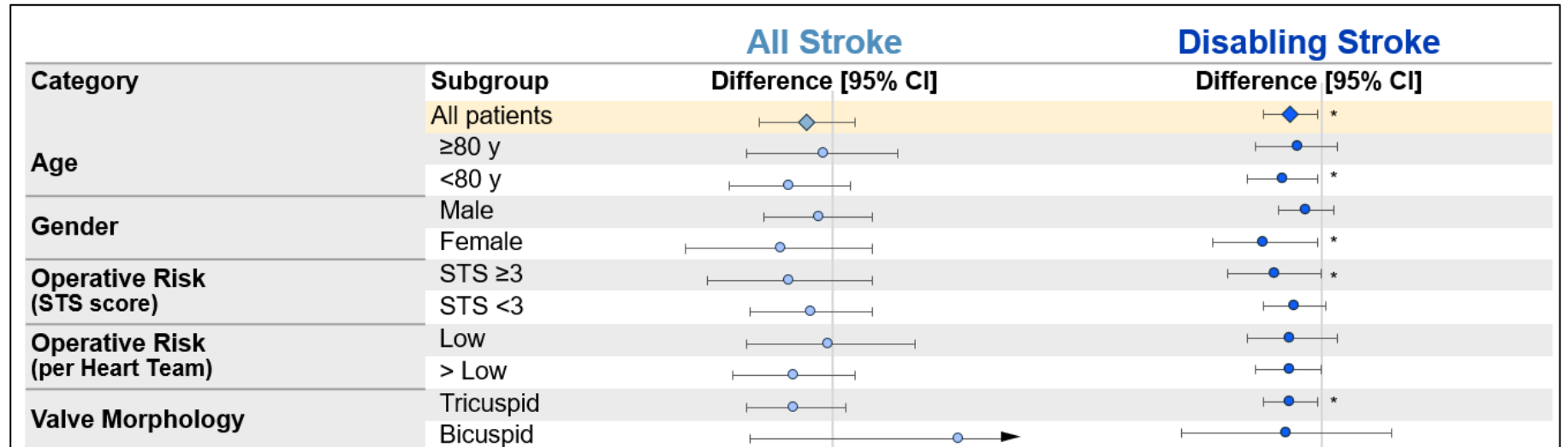
Predictors of In-Hospital Stroke after TAVR

Variable	Odds Ratio	P-Value
Age (per 5 yrs > 75 yrs old)	1.11	< 0.001
BSA (men/women; per m2)	0.55/0.43	< 0.001
GFR (per 5ml/min)	0.97	< 0.001
TA access	1.44	< 0.001
Non TA/TF access	1.77	< 0.001
Prior Stroke	1.57	< 0.001
Prior TIA	1.50	< 0.001
PAD	1.21	< 0.001
Smoker	1.28	0.008
Porcelain Aorta	1.23	0.04
Pre-procedure Shock	1.48	< 0.001

TVT Stroke Model

- Model derived from 97,600 TAVR procedures performed between 2014 and 2017

- Good calibration but poor discrimination (c-statistic 0.62)

- Implications: Patient selection likely to be challenging

PROTECTED TAVR:

Subgroup Analyses

Category	Subgroup	All Stroke Difference [95% CI]	Disabling Stroke Difference [95% CI]
	All patients		*
Age	≥80 y		
	<80 y		*
Gender	Male		
	Female		*
Operative Risk (STS score)	STS ≥3		*
	STS <3		
Operative Risk (per Heart Team)	Low		
	> Low		
Valve Morphology	Tricuspid		*
	Bicuspid		
Geographical Region	US		*
	OUS		

CEP better — Control better   CEP better — Control better

Implications

- Prediction of stroke in TAVR is challenging (and prediction of disabling stroke is almost impossible)

- There are only 2 rational strategies to using CEPD in TAVR– everyone or no one

Are there any subgroups that benefit?
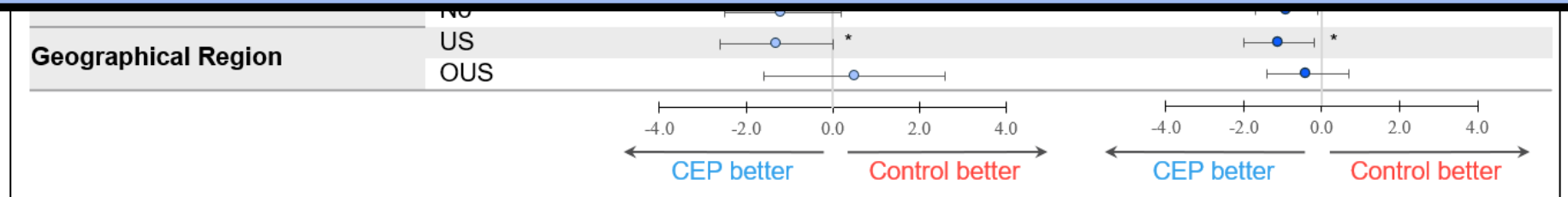
Summary

- Stroke remains a significant and unpredictable complication after TAVR

- Cerebroembolic protection devices capture procedure-related debris during the TAVR procedure and likely reduce volume of new brain lesions

- Clinical benefit of EPDs remains uncertain despite increasing use in the US → await definitive evidence from ongoing RCTs

- Selective use difficult to justify at present with the possible exception of ViV-TAVR and pts with bicuspid AS

- More research needed on long-term neurocognitive effects of non-disabling and clinically-silent strokes in TAVR and other structural cardiac procedures