TCTAP 2021 Virtual

Minimizing Embolic Events. Latest TAVR Data

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Disclosure

I, Eberhard Grube have the following financial interest/arrangement that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

Speaker Bureau/ SAB:
Medtronic, Boston Scientific, HighLife, Jena Valve

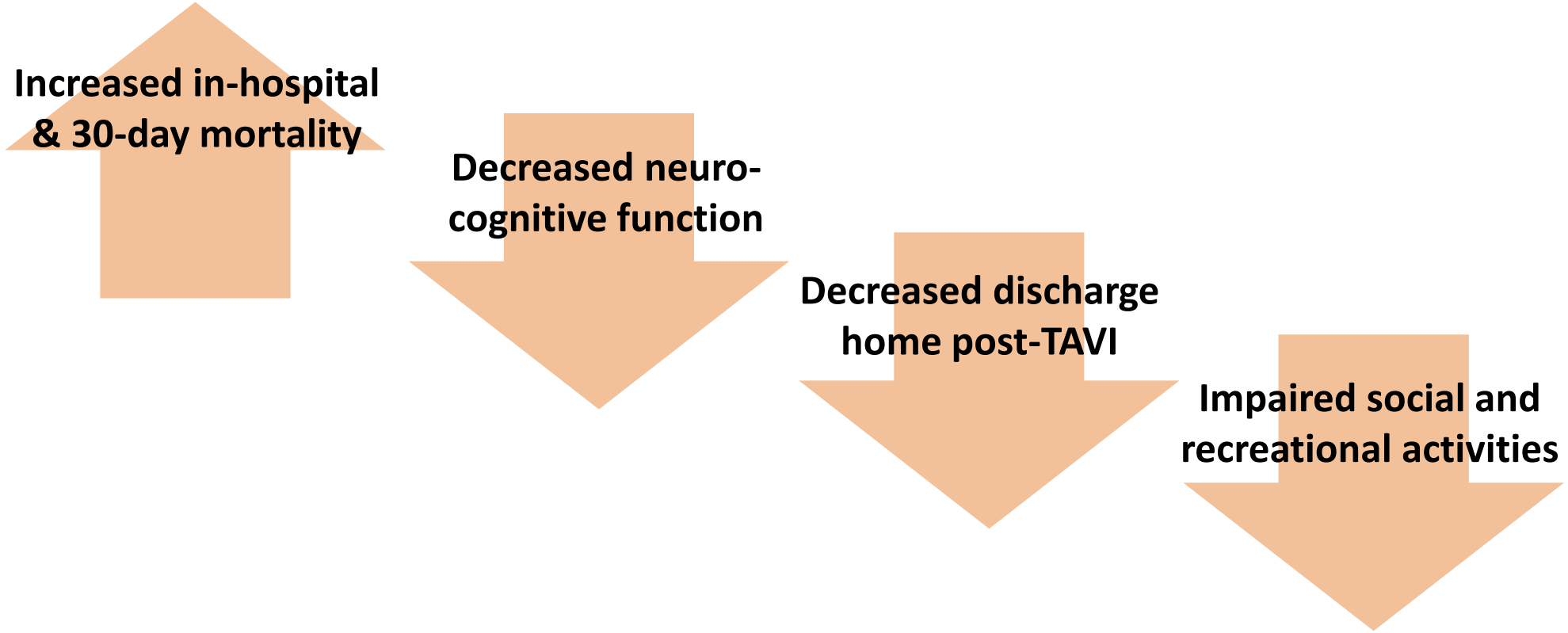
Equity Interest:
Cardiovalve, Claret, Shockwave, Valve Medical, CardioMech, Millipede, Imperative Care, Pie-Cardia, Ancora, Laminar, ReNiva

Stroke Outcomes

One of the most feared complications of TAVI

Post-TAVI stroke leads to poor outcomes for patients and their families. Although rates are low, reducing the risk of stroke remains an important concern for the future of the therapy.

Post-TAVI stroke is associated with:



[1]Huded, et al. JAMA 2019;321:2306-15. [1]Kapadia et al. Presented at TVT 2019.

Stroke Incidence

U.S. Registry reports ~2% stroke rate

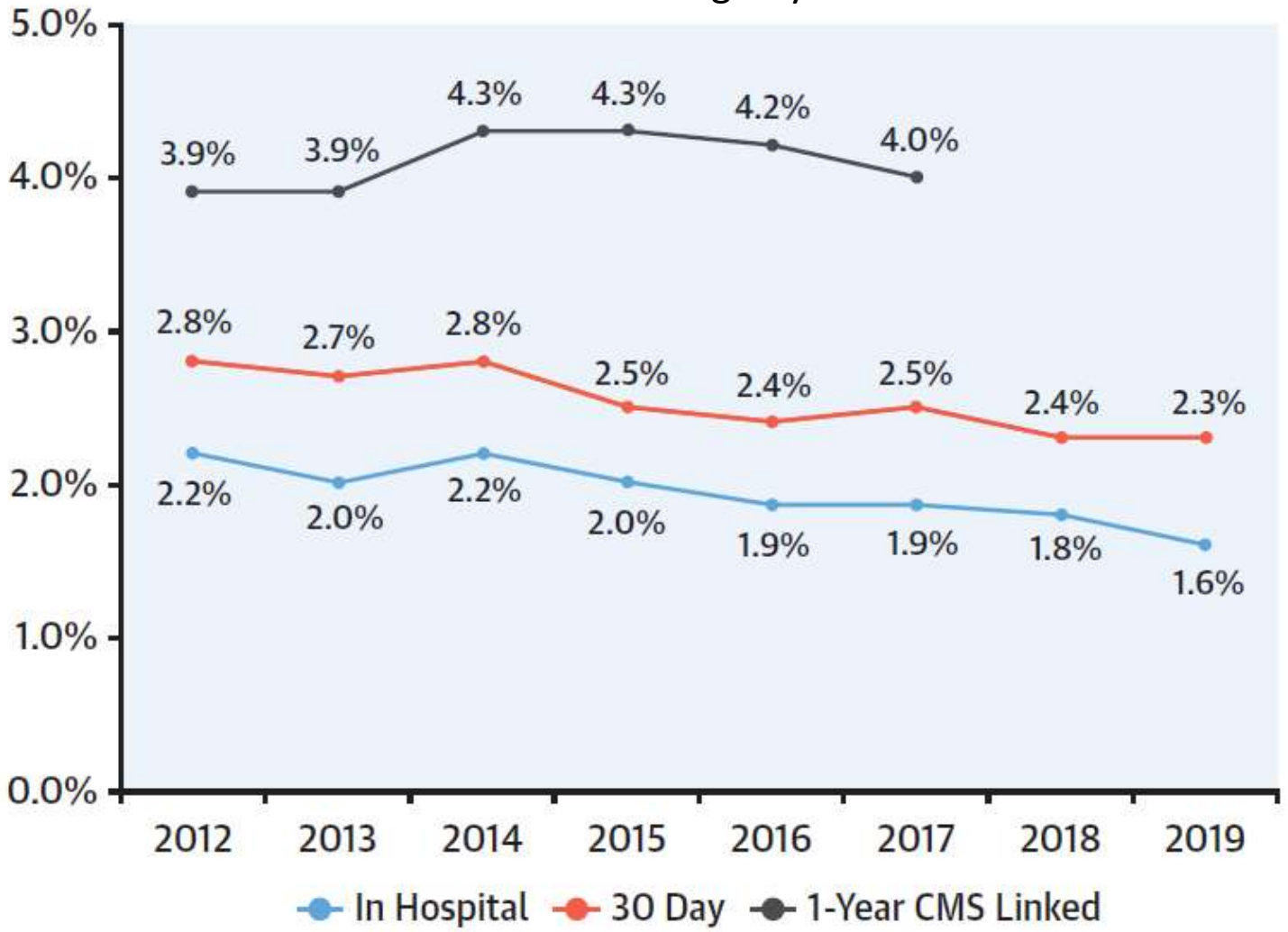
Registry data from 276,000+ U.S. patients show that the rate of 30-day stroke has **decreased slightly over time from 2.8% in 2012 to 2.3% in 2019.**

This likely reflects:

- **Changing patient demographics towards lower risk patients**
- **Increased operator experience**
- **Refined procedural techniques.**

Stroke Rates after TAVR

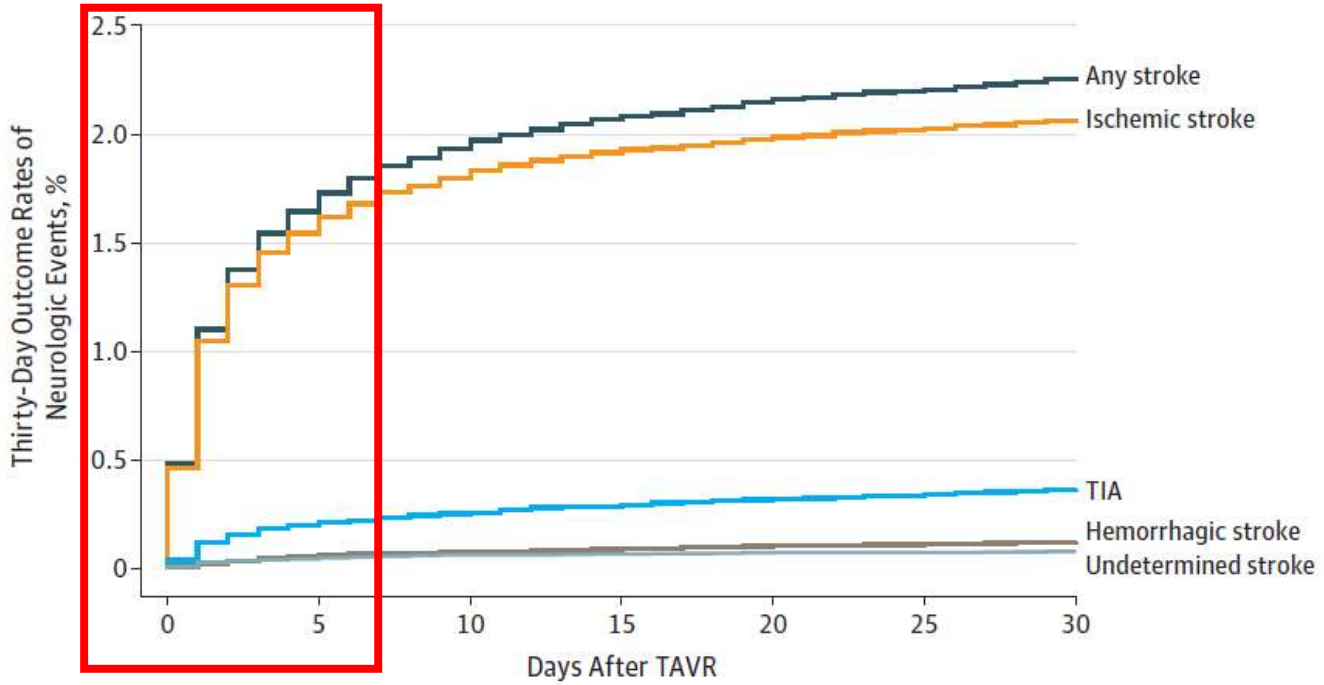
U.S. TVT Registry data



Stroke Incidence

Timing After TAVI

The greatest risk of stroke is in the immediate post-TAVI period. In an analysis of over 100,000 TAVI patients, the median time to stroke was 2 days.



No. at risk

Any stroke	101430	98245	97252	96654	96208	95855	86660
Ischemic stroke	101430	98329	97360	96770	96333	95983	86781
TIA	101430	99628	98762	98197	97747	97397	88068
Hemorrhagic stroke	101430	99781	98964	98425	97997	97661	88317
Undetermined stroke	101430	99785	98956	98423	98002	97667	88322

[1]Huded, et al. JAMA. 2019;321(23):2306-2315.

Stroke Risk Factor
Baseline Calcium Volume

Greater aortic valve calcification is related to increased microemboli released during TAVI. However, calcium is not the only material debris that embolizes during a TAVI procedure.

TABLE 4 Correlations between high intensity transient signals (HITS) and calcium score

Correlation	Spearman's correlation	*p* value
Solid HITS vs valve calcium score	0.319	0.033
Gaseous HITS vs valve calcium score	0.162	0.289
Solid HITS vs root calcium score	−0.170	0.263
Gaseous HITS vs root calcium score	−0.078	0.612
Solid HITS valve positioning vs valve calcium score	0.315	0.035
Gaseous HITS valve positioning vs Valve calcium score	0.290	0.053

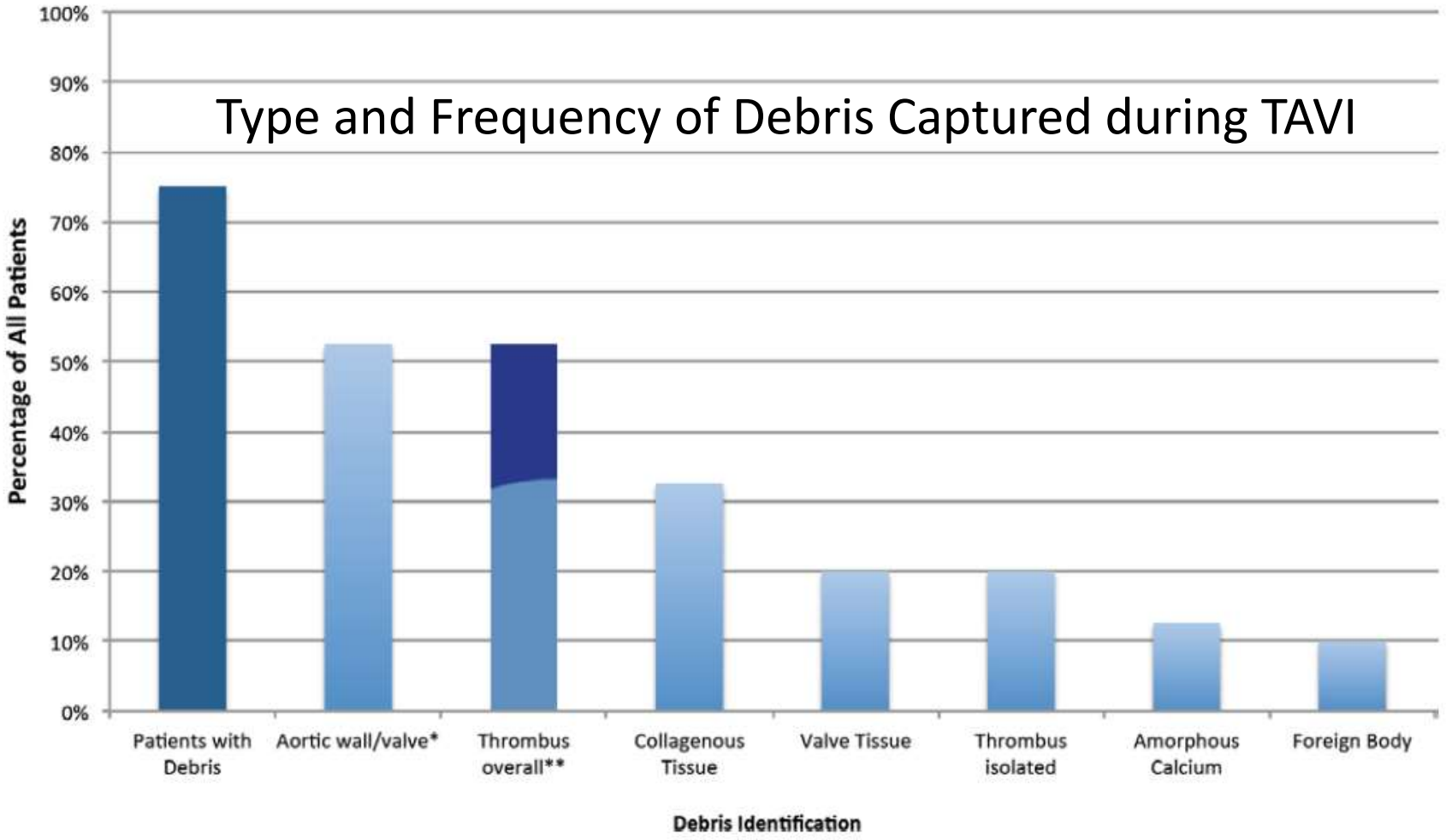
Significant values are highlighted in bold.

Procedure-related Embolic Events

Embolized debris beyond calcium

Based on histological analysis of debris captured with cerebral embolic protection during TAVI, embolized debris commonly includes:

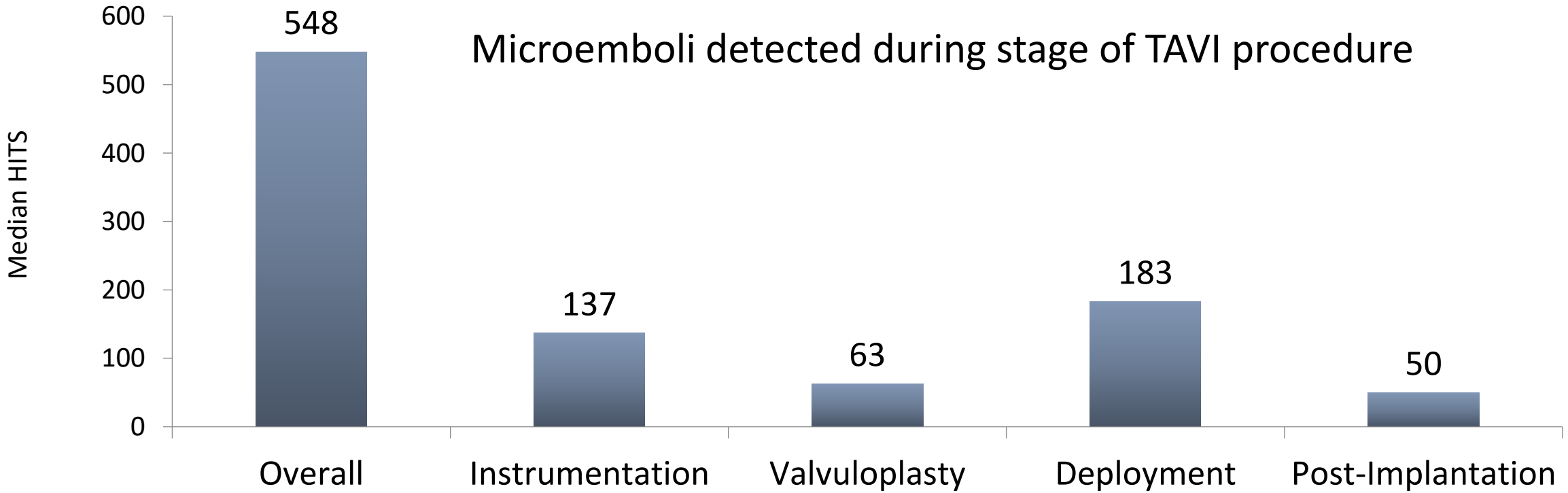
- **Native aortic wall/valve tissue**
- **Thrombus**
- **Polymer debris from catheters**



Procedure-related Embolic Events

Microemboli detected at all stages of TAVI procedure

- Although data are limited to small patient numbers, these studies show microemboli can be detected using transcranial Doppler during each step of the TAVI procedure.
- This suggests that debris can be embolized by friction between the wires, balloons, valve, or catheters and the native anatomy.



Erdoes, et. al. , Eur J Cardiothorac Surg 2012; 41:778-83

Procedure-related Embolic Events

Microemboli detected at all stages of TAVI procedure

The **top procedural steps** associated with emboli **are valve positioning, crossing the valve, or exchanging catheters.**

TABLE 3 Number of solid and gaseous emboli occurring at each time point during TAVI

		Solid	Gaseous
Time point	*n*=	Median (IQR)	Median (IQR)
Insertion of diagnostic catheters	61	4.0 (0.5-14.0)	11.5 (3.0-44.5)
Cross valve/exchange catheters	63	15.0 (6.0-33.5)	61.0 (26.0-99.0)
Insert balloon	30	1.75 (0.9-3.0)	6.25 (2.8-9.0)
Balloon valvuloplasty	30	3.25 (1.8-9.3)	15.0 (6.1-39.1)
Valve transition through arch	54	1.0 (0.0-1.6)	3.25 (0.0-8.6)
Valve positioning	63	27.0 (16.5-40.5)	86.0 (57.5-127.5)
Valve deployment	62	2.5 (0.5-10.3)	8.0 (2.0-41.1)
Remove delivery system	59	7.5 (4.0-13.0)	23.5 (11.0-42.0)
Late emboli	55	5.0 (1.5-10.0)	22.5 (6.0-30.0)
Total	63	76.0 (61.0-112.0)	278.5 (202.0-372.0)

Aggarwal, et al. J interv Cardiol 2018;31:646-54.

Procedure-related Embolic Events

Must prioritize patient outcomes over microemboli risk

The observed presence of microemboli did not impact stroke rates, with zero stroke events recorded during the study.

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Proper positioning and use of post-dilation when necessary to avoid moderate/severe PVL and pop-out should of course be prioritized over concerns of silent microemboli.

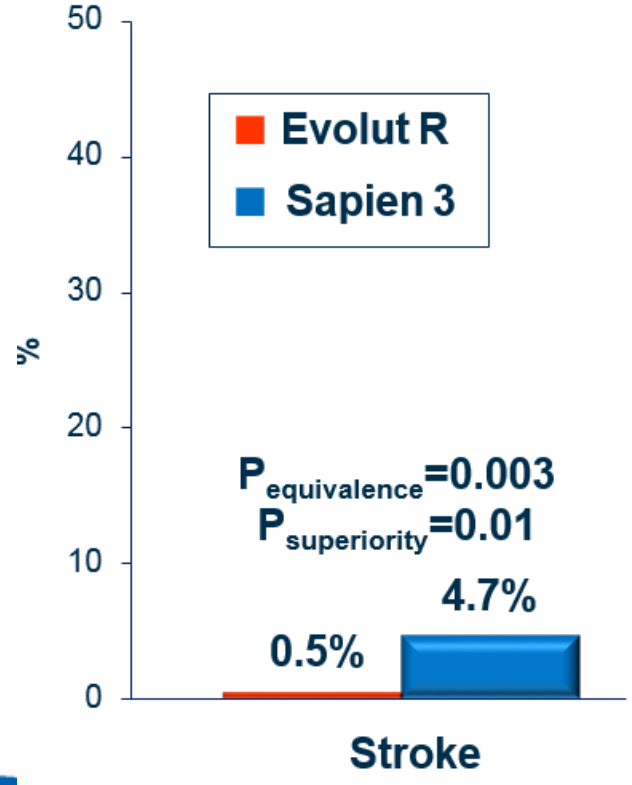
Aggarwal, et al. J interv Cardiol 2018;31:646-54.

Considerations for Stroke Prevention

Valve design and features

The only randomized trial to date comparing contemporary balloon- and self-expanding valves (SOLVE TAVI) demonstrated a significantly lower rate of stroke in the self-expanding Evolut R cohort at 30 days.

This difference may have been related to less experience among operators with the balloon-expandable valves.



Baseline Characteristics – Valve Strategy SOLVE-T

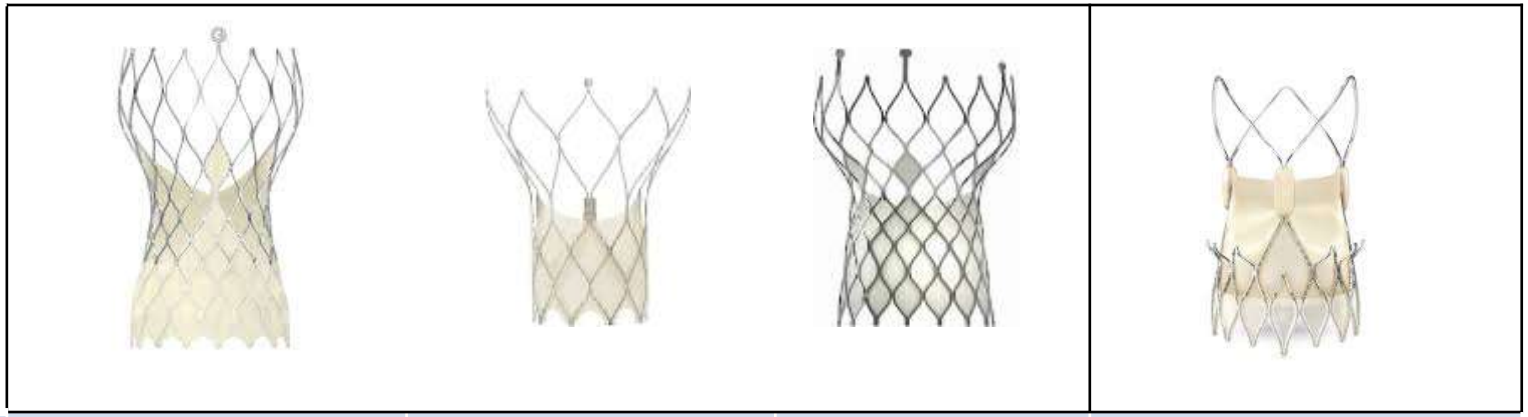
Characteristic	Evolut R (n=219)	Sapien 3 (n=219)
Age (years); mean ±SD	81.7 ±5.3	81.5 ±5.7
Male sex; n/total (%)	105/219 (47.9)	109/219 (49.8)
Risk scores		
STS score (%); mean ±SD	7.7 ±7.2	7.6 ±7.4
Log. EuroScore I (%), mean ±SD	18.4 ±12.1	18.3 ±13.1
EuroScore II (%), mean ±SD	6.1 ±5.5	5.4 ±4.9
Frailty; n/total (%)	93/216 (43.1)	80/217 (36.9)
Peripheral arterial disease; n/total (%)	28/219 (12.8)	27/219 (12.3)
Prior myocardial infarction; n/total (%)	19/219 (8.7)	22/219 (10.1)
Prior PCI; n/total (%)	84/219 (38.4)	79/219 (36.1)
Prior CABG; n/total (%)	26/219 (11.9)	18/219 (8.2)
Atrial fibrillation; n/total (%)	103/219 (47.0)	93/219 (42.5)
Pacemaker/ICD; n/total (%)	24/218 (11.0)	23/219 (10.5)
Prior stroke; n/total (%)	25/219 (11.4)	26/218 (11.9)

Thiele, et al. SOLVE TAVI. Presented at TCT 2018

Considerations for Stroke Prevention

Valve design and features

Recapturability is a key benefit among contemporary self-expanding TAVI devices. Around 30% of TAVI cases in the Evolut Low Risk trial used the recapture feature, and up to 40% of Portico TAVI cases have reported using recapturability.



	Evolut PRO	Portico	Venus A	Acurate neo
Recapturable	**Yes**	**Yes**	**Yes**	**No**

Attizzani, et al. JACC Interv 2020;13:1816–24.

Considerations for Stroke Prevention

Recapturability not associated with increased risk of stroke

Although valve deployment has been associated with release of microemboli in small studies, recapture and redeployment was not associated with increased stroke in the Evolut Low Risk Trial.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 13, NO. 15, 2020

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Impact of Repositioning on Outcomes Following Transcatheter Aortic Valve Replacement With a Self-Expandable Valve

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ABSTRACT

OBJECTIVES This study sought to compare outcomes following transcatheter aortic valve replacement when valve repositioning was performed (repositioned group) versus procedures without repositioning (nonrepositioned group).

BACKGROUND The Evolut R and Evolut PRO valves were designed to allow repositioning during deployment, yet the effect of repositioning on clinical outcomes remains unclear.

METHODS Patients implanted with the Evolut R or PRO valve from the SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial continued access study and the Evolut Low Risk Trial between June 2016 and November 2018 were combined. Baseline multidetector computed tomography data were analyzed for the Evolut Low

TABLE 6 Clinical Events Through 30 Days

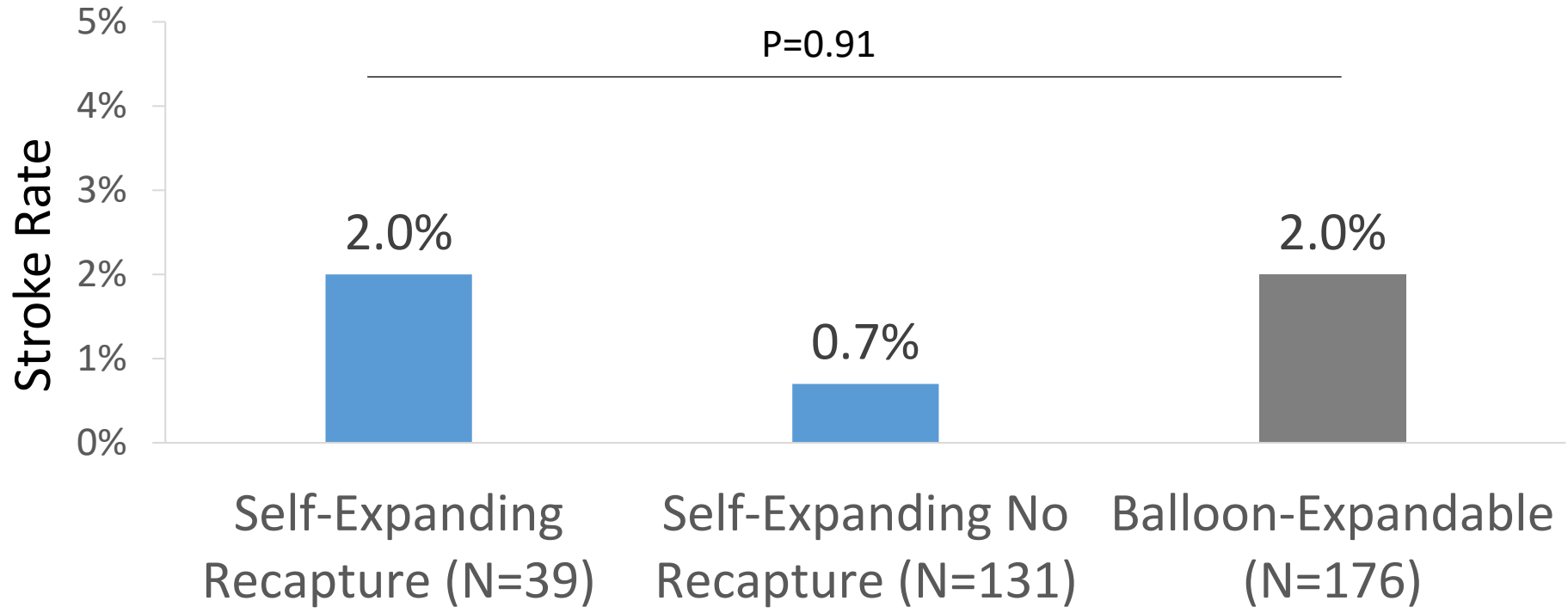
	All Patients (N = 946)	Repositioned Group (n = 318)	Nonrepositioned Group (n = 628)	p Value*
All-cause mortality	3 (0.3)	1 (0.3)	2 (0.3)	0.99
All stroke	28 (3.0)	13 (4.1)	15 (2.4)	0.15
Disabling stroke	4 (0.4)	1 (0.3)	3 (0.5)	0.71
Nondisabling stroke	24 (2.7)	12 (3.9)	12 (2.0)	0.09
Major vascular complication	34 (3.6)	9 (2.8)	25 (4.0)	0.37
Life-threatening or disabling bleeding	17 (1.8)	8 (2.5)	9 (1.4)	0.24
Stage 2 or 3 acute kidney injury	10 (1.1)	7 (2.2)	3 (0.5)	0.01
Coronary obstruction	6 (0.6)	5 (1.6)	1 (0.2)	0.01
Reintervention	2 (0.2)	2 (0.6)	0 (0.0)	0.05
Permanent pacemaker implantation†	157 (17.3)	59 (19.1)	98 (16.3)	0.26

Attizzani, et al. JACC Interv 2020;13:1816–24.

Considerations for Stroke Prevention

Recapturability not associated with increased risk of stroke

A recent single-center study found no significant difference in stroke rates between self-expanding TAVI with recapture, self-expanding TAVI without recapture, and balloon-expandable TAVI.



Considerations for Stroke Prevention

Cerebral embolic protection devices

Transcatheter neuroprotection during TAVI is a high-interest subject for patients and clinicians, though clinical evidence on effectiveness of stroke prevention is lacking.

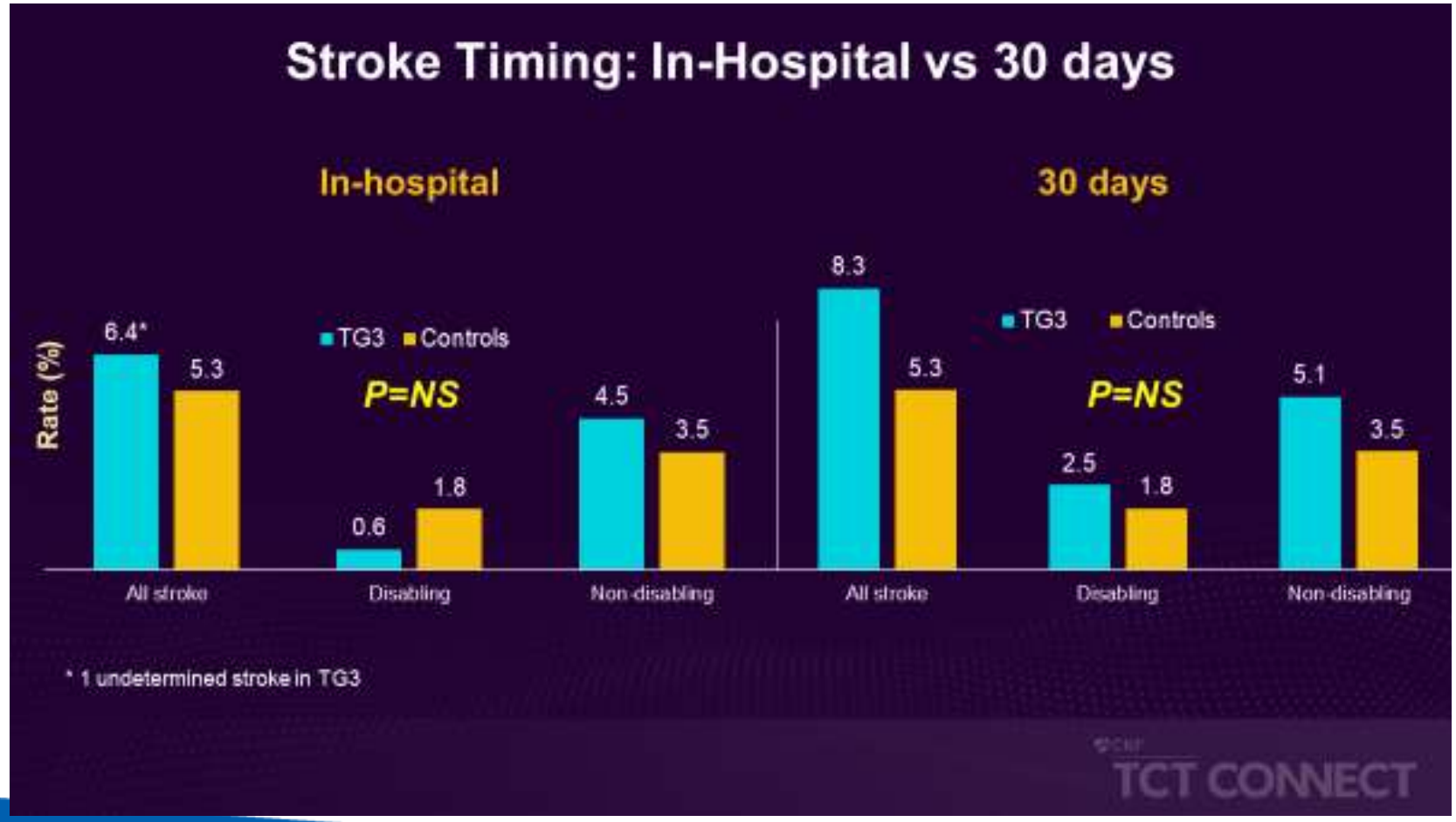
Several devices are currently under investigation. Sentinel is currently the only device with CE mark and U.S. FDA approval.

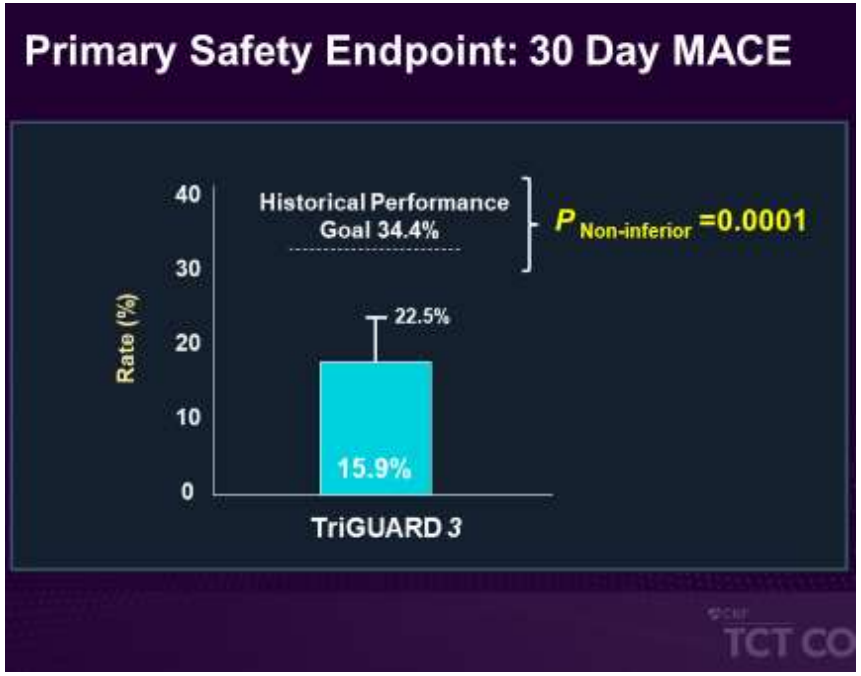
Claret Medical Sentinel	Keystone TriGuard	Edwards Embrella	ICS Emblok
			

Considerations for Stroke Prevention

Cerebral embolic protection devices/Triguard

The REFLECT study randomized patients to TAVI alone or TAVI with the TriGuard cerebral protection device and **found similar rates of in-hospital stroke and 30-day stroke** compared to controls. Use of CEP did meet the safety threshold for MACE events at 30 days.



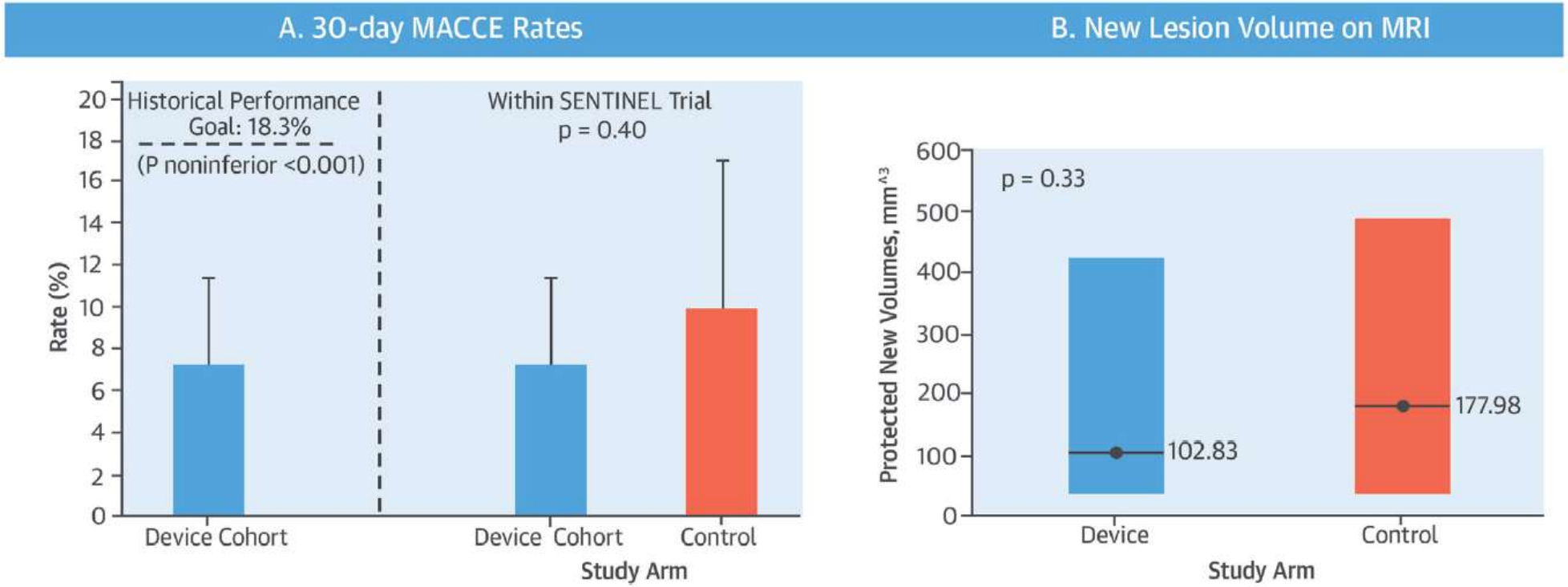


Moses. Presented at TCT 2020.

Considerations for Stroke Prevention

Cerebral embolic protection devices/Sentinel

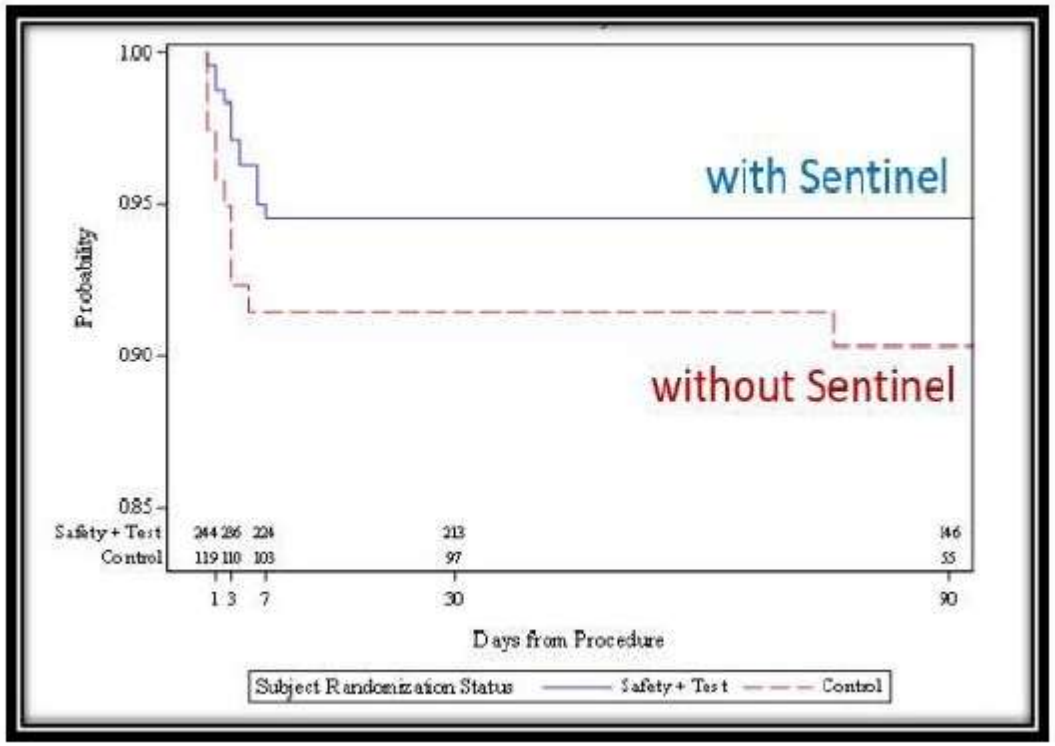
Similarly, the Sentinel embolic protection device met the MACCE safety endpoint and demonstrated a lower total volume of brain lesions compared to TAVI without CEP.

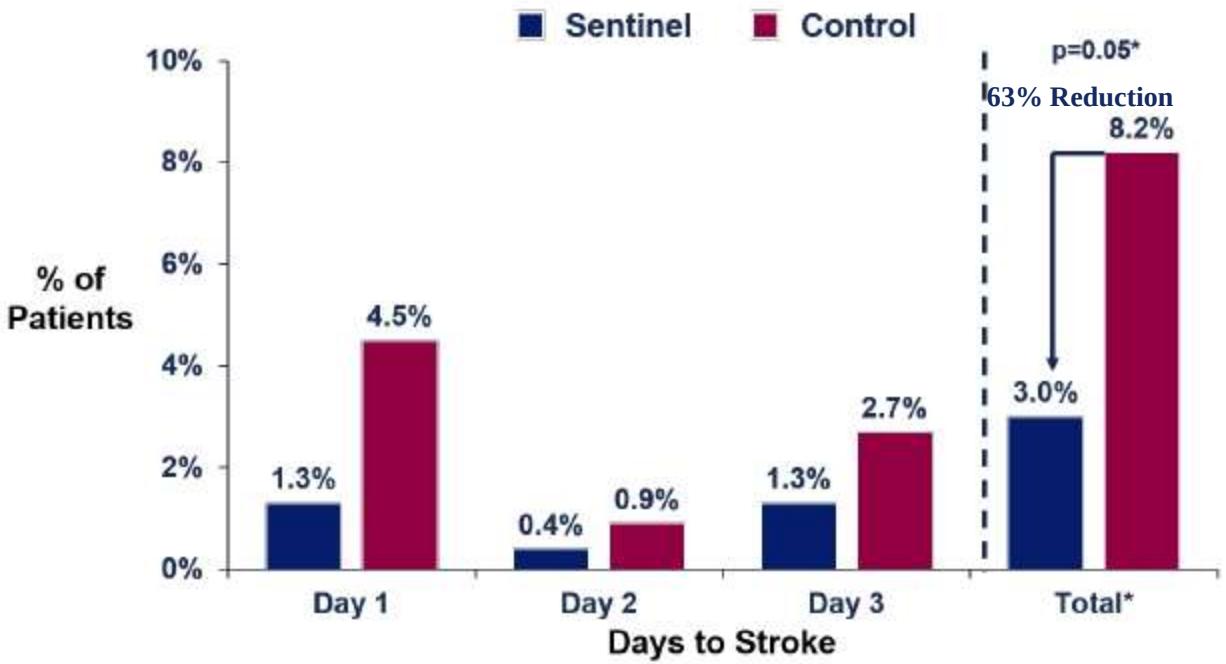


Kapadia, S.R. et al. J Am Coll Cardiol. 2017;69(4):367-77.

Considerations for Stroke Prevention

Cerebral embolic protection devices/Sentinel





95% of SENTINEL patients were evaluated by neurologists
Clinical Events Committee included 2 stroke neurologists

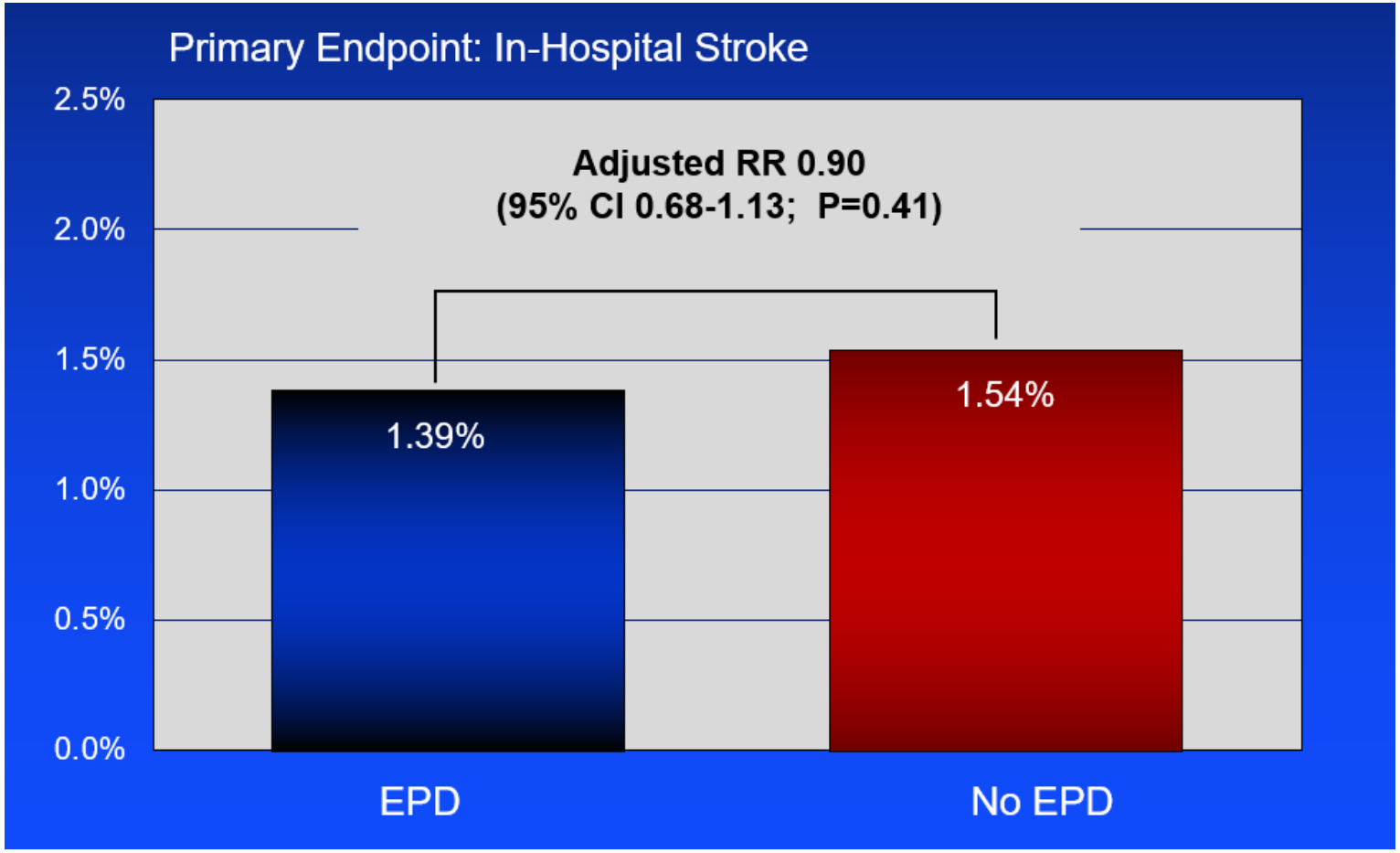
***Fisher Exact Test**

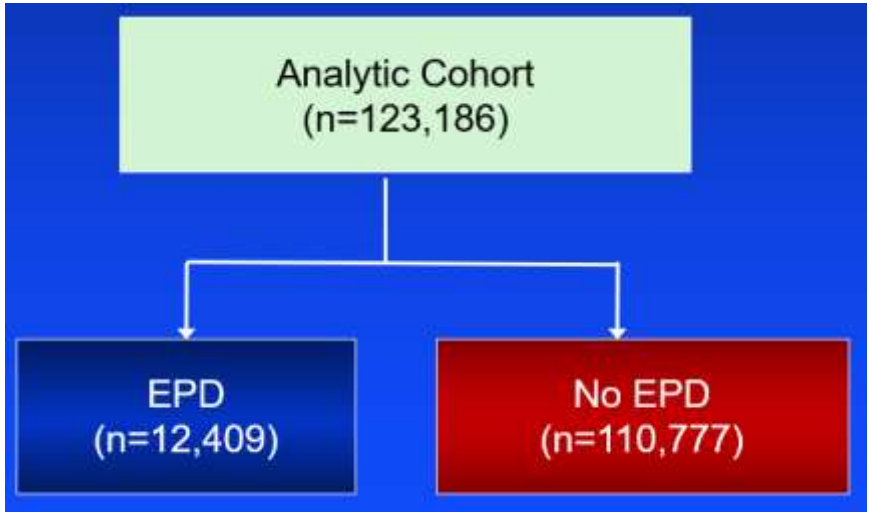
SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

Considerations for Stroke Prevention

Cerebral embolic protection devices

A large study from the U.S. TVT Registry analyzing 123,000+ total patients showed no difference in stroke between those using CEP and those who did not.





Cohen. Presented at TCT Connect 2020.

Considerations for Stroke Prevention

Selective CEP use

The current evidence still demonstrate the safety of these CEP devices.

Implanters may choose to continue CEP use for the apparent advantage of captured debris

Use of CEP varies widely across institutions. In the absence of data showing efficacy, some operators may consider using embolic protection selectively in patients who may be at higher risk of stroke/TIA events.

Selective CEP Use

Operators may consider using CEP in patients with:

- **Bicuspid aortic valve / V-in-V**
- **Highly calcified valve or aorta**
- **History of stroke**

Considerations for Stroke Prevention

Need for a large, randomized study on CEP

There is still a need for a large, randomized study and use of embolic protection.

The randomized PROTECTED TAVR Trial is currently investigating TAVI outcomes with or without use of the approved Sentinel device. The primary endpoint is stroke events within 72 hours of TAVI.

PROTECTED TAVR

Randomized, prospective trial

N=3,000

Primary Completion: June 2022

Considerations for Stroke Prevention

Need further study on “silent” brain lesions and long-term cognitive impact

While several methods of quantifying microemboli and subclinical brain lesions have been used in embolic protection studies to date, we do not yet have robust data on what size or location of lesion may have the most clinical impact to the patient.

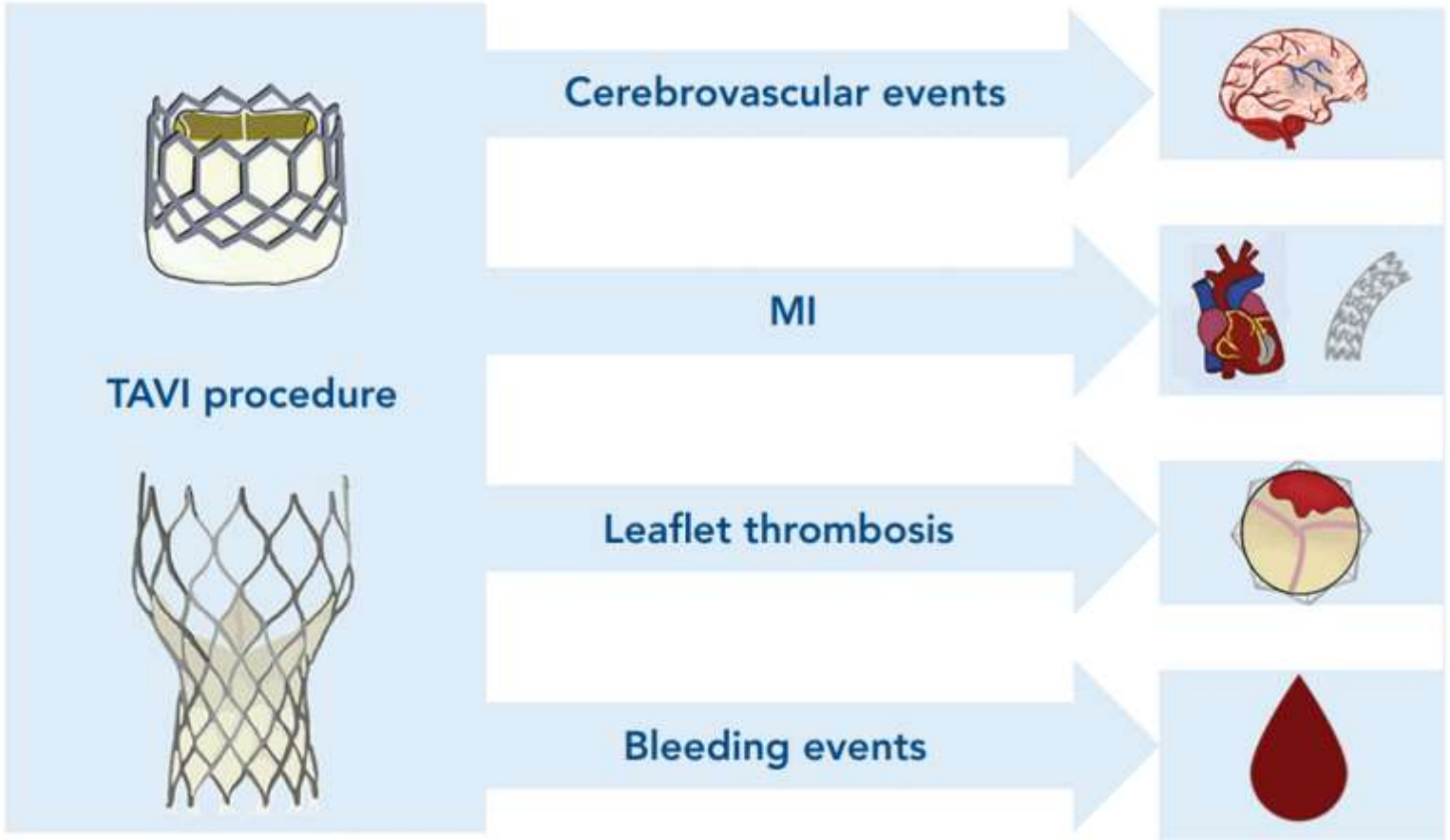
Identifying thresholds or markers of subclinical lesions that may affect patients’ neurocognition in the long term would help ascertain utility of CEP devices in these younger, lower risk patient population beyond overt reduction in stroke.

Methods of assessing microemboli and brain lesions
Brain lesion volume by diffusion-weighted MRI
High-intensity transient signals (HITS) detected by transcranial Doppler
Debris volume (mm^3)

Antithrombotic Regimen

Antiplatelet and Anticoagulation

Antithrombotic regimen is another key piece of maintaining a low risk of stroke. The optimal antithrombotic regimen for TAVI patients is largely undefined, as it must balance the risk of bleeding and other patient outcomes.



[1]Makkar, presented at TCT 2017; [2]Jose et al., JACC Interv. 2017;10:686-97; [3]Chakravarty et al. Lancet. 2017;389:2383-92. [4]Hansson et al. JACC 2016;68:2059-69. [5]Overtchouk, et al. JACC 2019:73;13-21. Lugo et al. European Cardiology Review 2020;15:e09.

Antithrombotic Regimen Post-TAVI

U.S. and EU. guidelines

The current European Society of Cardiology and ACC/AHA guidelines (last updated in 2017), recommend dual antiplatelet therapy for the first 3-6 months post-TAVI, or single antiplatelet therapy in patients at high risk of bleeding as Class 2b recommendation

Guideline	Recommendations	Class and Level of Evidence
ESC/EACTS guidelines (2017)	Dual antiplatelet therapy should be considered for the first 3–6 months after TAVI, followed by lifelong single antiplatelet therapy in patients who do not need oral anticoagulation for other reasons	IIa, C
	Single antiplatelet therapy may be considered after TAVI in the case of high bleeding risk	IIa, C
ACC/AHA guidelines (2017 Update)	Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily	IIb, B-NR
	Anticoagulation with a VKA to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding	IIb, C

Lugo et al. European Cardiology Review 2020;15:e09

Antithrombotic Regimen Post-TAVI

U.S. guidelines now recommend SAPT (Class 2a level of evidence)

The recently updated ACC/AHA antithrombotic guidelines now include single antiplatelet therapy (SAPT) as a reasonable post-TAVI regimen in most patients, informed by the ARTE randomized trial and recent meta-analyses demonstrating similar efficacy with SAPT compared to dual antiplatelet therapy, but with decreased risk of major bleeding events.

The guidelines also highlight results from the GALILEO trial, which was halted early for increased safety risk in patients taking rivaroxaban plus aspirin post-TAVI.

2a	B-R	5. For patients with a bioprosthetic TAVI, aspirin 75 to 100 mg daily is reasonable in the absence of other indications for oral anticoagulants (12–14).
2b	B-NR	10. For patients with a bioprosthetic TAVI who are at low risk of bleeding, dual-antiplatelet therapy with aspirin 75 to 100 mg and clopidogrel 75 mg may be reasonable for 3 to 6 months after valve implantation (12,13,29).
3: Harm	B-R	12. For patients with bioprosthetic TAVI, treatment with low-dose rivaroxaban (10 mg daily) plus aspirin (75–100 mg) is contraindicated in the absence of other indications for oral anticoagulants (30).

Otto et al. JACC 2020; ePub

Antithrombotic Regimen Post-TAVI

Ongoing studies

The key balancing act for post-TAVI antithrombotic regimen is to mitigate risk of thromboembolic events and valve thrombosis without introducing elevated bleeding risk.

No other indication for OAC

Antiplatelet-based strategies

PTOLEMAIOS
(aspirin + ticagrelor versus aspirin + clopidogrel)

TIC TAVI
(ticagrelor versus aspirin+ clopidogrel)

Anticoagulant-based strategies

GALILEO
(aspirin + rivaroxaban versus aspirin + clopidogrel)

AUREA
(VKA versus aspirin + clopidogrel)

ADAPT-TAVR
(edoxaban versus aspirin + clopidogrel)

LRT 2.0
(aspirin + VKA versus aspirin)

With or without indication for OAC

Antiplatelet and anticoagulant-based strategies

POPular-TAVI
(aspirin + clopidogrel versus aspirin/ OAC + clopidogrel versus OAC)

Anticoagulant-based strategies

ATLANTIS
(apixaban versus aspirin ± clopidogrel/ apixaban versus VKA)

Indication for OAC

Anticoagulant-based strategies

AVATAR
(OAC versus aspirin + OAC)

ENVISAGE-TAVI AF
(edoxaban versus VKA)

There are several ongoing trials that aim to further define proper antithrombotic strategies for TAVI patients.

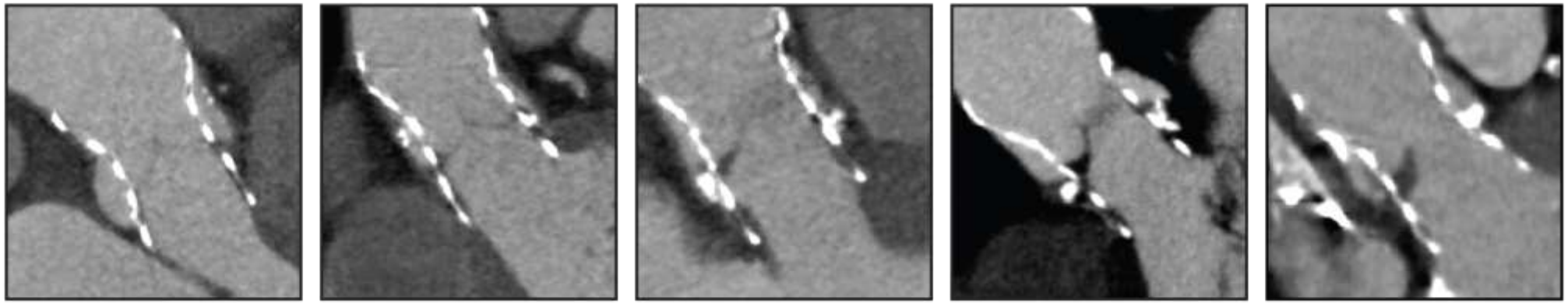
Lugo et al. Eur Cardiol Rev 2020;15:e09.

Considerations for Longer-term Stroke Risk

Subclinical thrombosis/HALT

Subclinical leaflet thrombosis, also known as HALT, is relatively common after TAVI and SAVR. An early study from the RESOLVE registry showed HALT may be associated with risk of stroke/TIA, recent larger studies have not supported this finding.

The HALT substudies conducted within the randomized PARTNER 3 and Evolut Low Risk trials included prospective CT follow-up at 30 days and 1-year post-TAVI and **did not show an association between HALT and increased stroke/TIA events.**



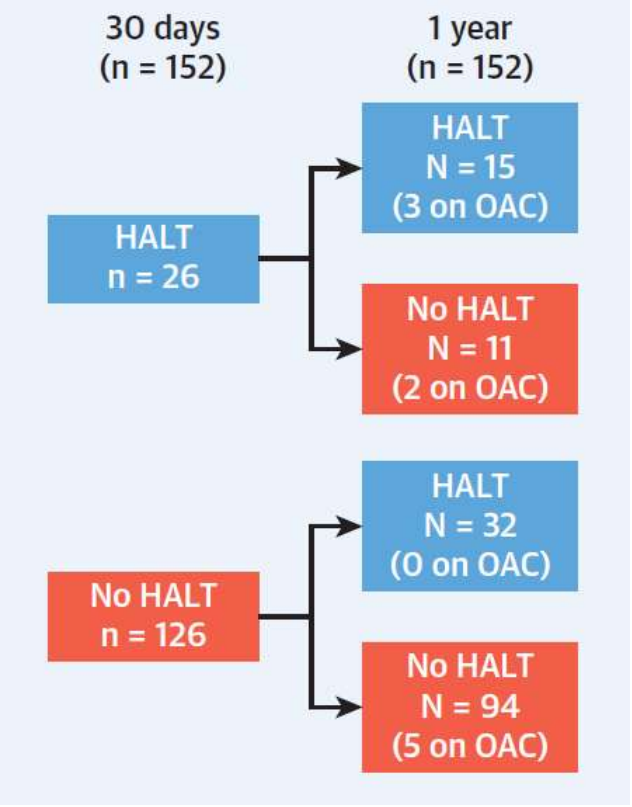
Makkar RR, et al. N Engl J Med 2015; 373:2015-24. Chakravarty, et al. Lancet 2017; 389:2383-2392. Blanke JACC 2020;75:2430–42. Makkar, JACC 2020;75:3003–15

Considerations for Longer-term Stroke Risk

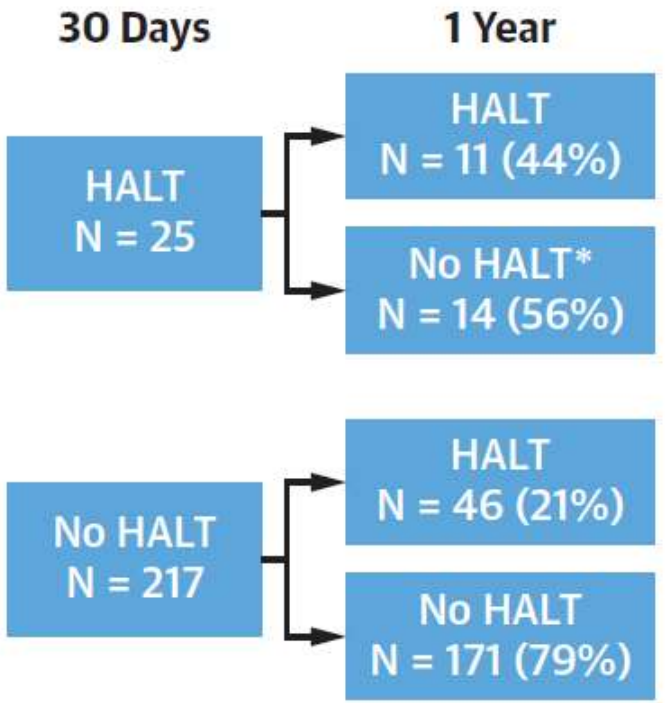
Subclinical thrombosis

We also know that subclinical thrombosis is a dynamic phenomenon: HALT can resolve spontaneously and may appear 1 year after TAVI or later.

Evolut Low Risk CT Substudy



PARTNER 3 CT Substudy



Blanke JACC 2020;75:2430–42; Makkar JACC 2020;75:3003–15.

Minimizing Embolic Events

Summary of Evidence

- Rates of stroke have declined slightly over the past 5 years, but stroke prevention remains an important area for improving patient outcomes post-TAVI.
- Most TAVI-related strokes occur within the first few days after the procedure, affecting approximately 2% of patients.
- Subclinical ischemic lesions occur at all stages of the TAVI procedure, but the clinical impact and long term prognosis of these silent infarcts are unknown.
- Embolic protection devices are being studied for reducing risk of stroke and can be considered safe in TAVI patients. They might be used in a certain subset of patients
- Optimal antithrombotic regimen and the significance of HALT/subclinical leaflet thrombosis are still undefined.

Thank you for your kind attention!