CEP in TAVR – From Rationale, Practical Viewpoint and Data Updates

AP Valves & Structural Heart Summit 2023 August 10-11

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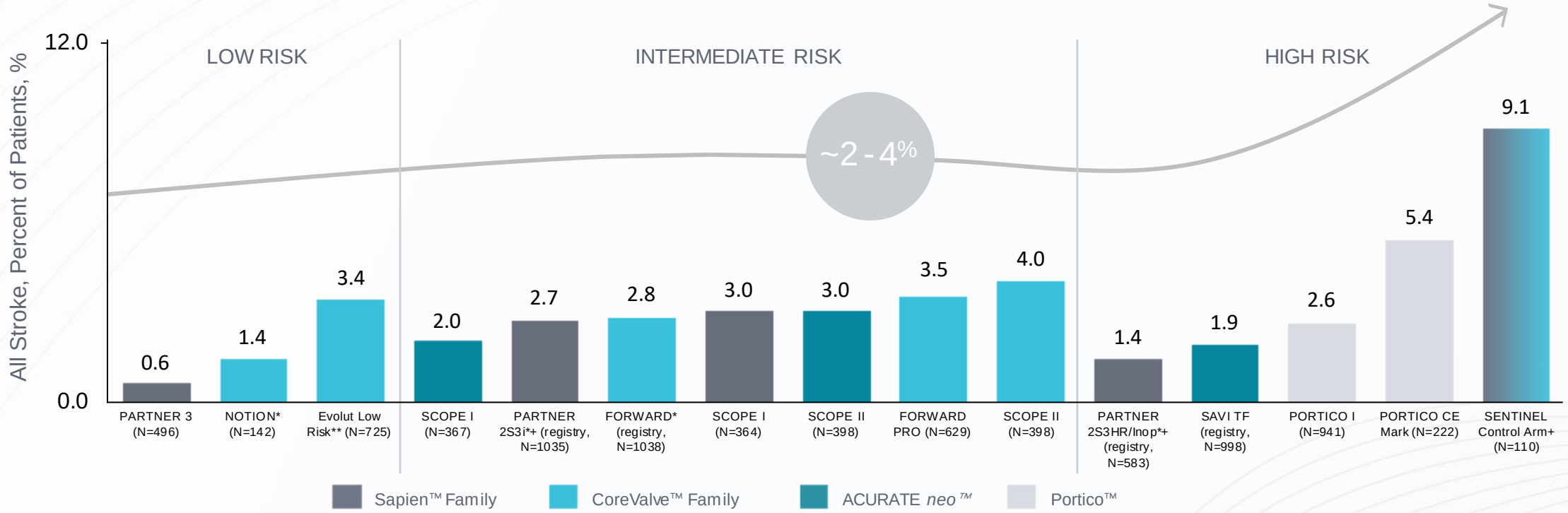
Disclosure

- None

Contemporary Studies Show Consistent Rate of Stroke



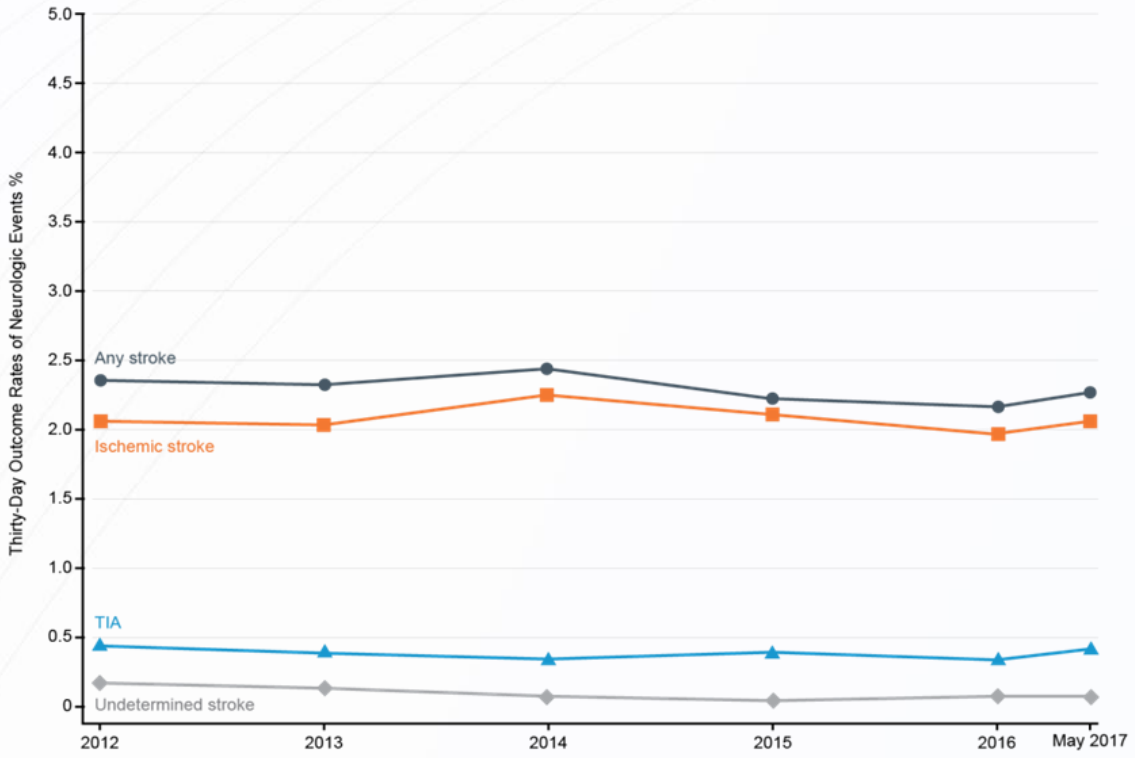
*Kaplan Meier estimates; **Bay esian estimate; PA=phy sician assistant; NP=nurse practitioner; SENTINEL: Kapadia JACC 2017 (95% of patients were ev aluated pre- and post-TAVR by neurologists, and stroke neurologists were on the CEC); Ev olut Low Risk: Popma NEJM 2019 (<2% of TAVR patients receiv ed an embolic protection dev ice); PARTNER 3: Mack NEJM 2019; PORTICO CE Mark: Linke, Circ Cardiov asc Interv 2018 (Supplement); ; PORTICO I: Sondergaard JACC 2018; FORWARD: Grube, JACC 2017 (an embolic protection dev ice was used in 4.1% of patients); FORWARD PRO: Grube, PCR 2019 (an embolic protection dev ice was used in 9.1% of patients); PARTNER 2S3i: Thourani, Lancet 2016; PARTNER 2S3HR/Inop: Kodali Eur Heart J 2016; SCOPE I: Lanz, Lancet 2019; SAVI TF: Möllmann, EuroInterv ention 2018; NOTION: Thy regod JACC 2015; Tamburino Circulation 2020

Results from diff erent studies are not directly comparable. + Study protocol included mandated, per-protocol baseline and follow-up ev aluation by neurologist, neurology PA, neurology NP or neurology f ellow. Inf ormation prov ided f or educational purpose only.

For more inf ormation on the underdiagnosis of Stroke, click here

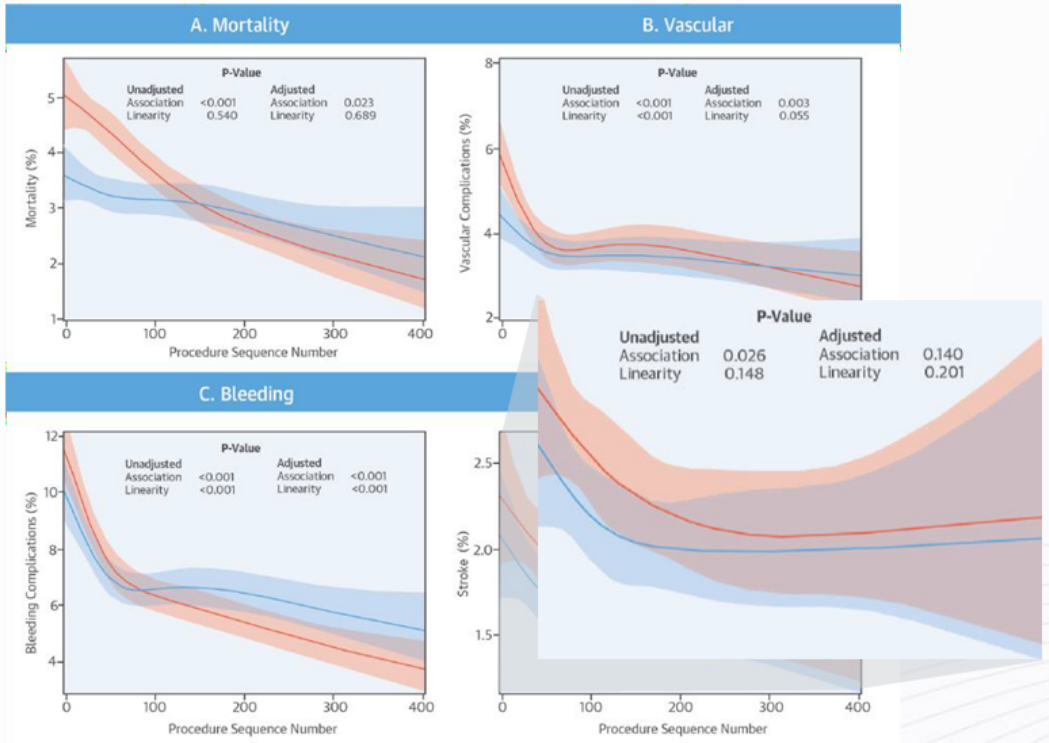
TAVI and Stroke Rates

Consistent Stroke Occurrence Despite Newer Technologies

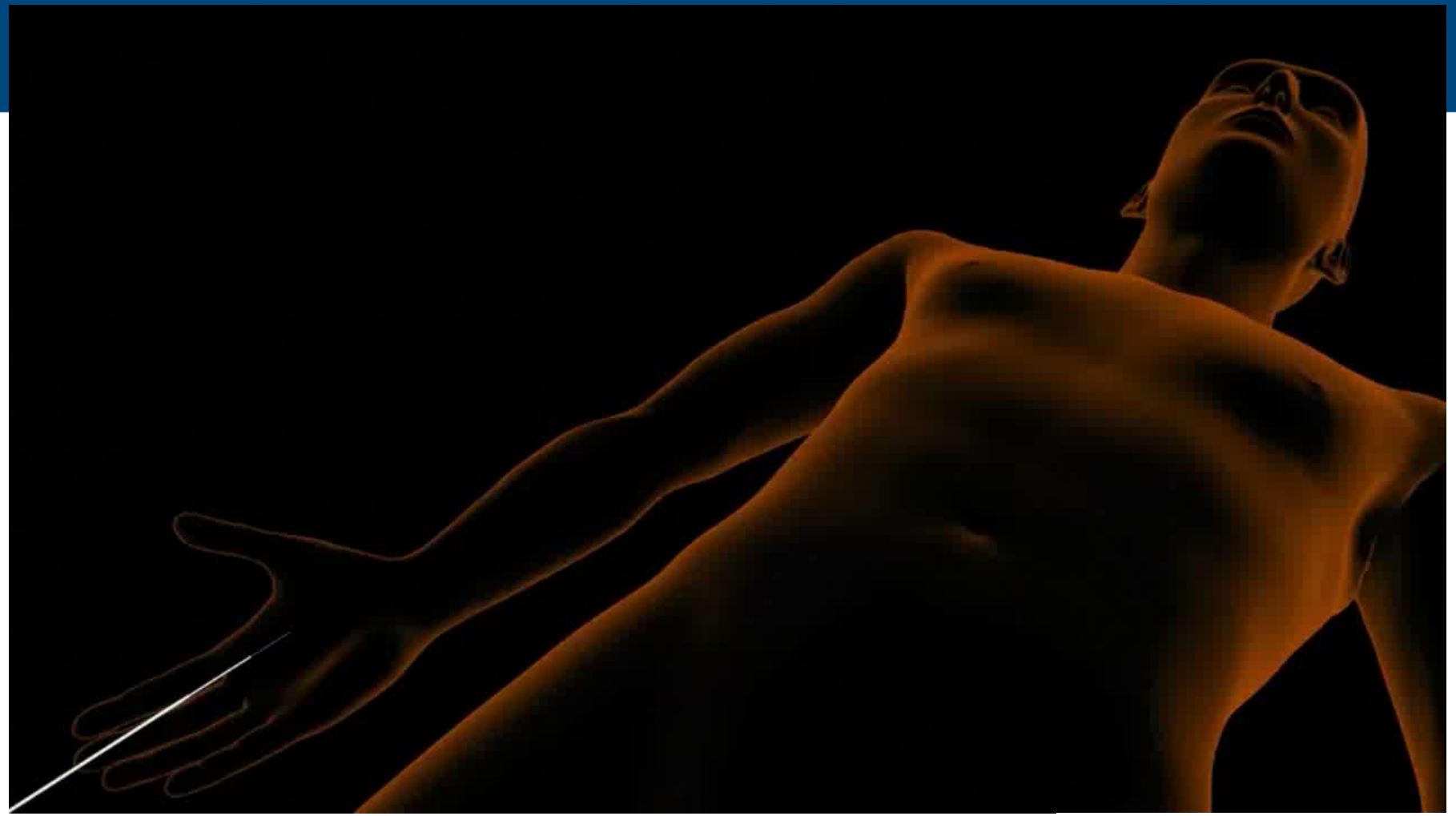


Huded CP, Tuzcu EM, Krishnaswamy A, et al. Association Between Transcatheter Aortic Valve Replacement and Early Postprocedural Stroke. JAMA. 2019;321(23):2306–2315. doi:10.1001/jama.2019.7525

TAVR Complications Have Improved Over Time With the Exception of Stroke



Carroll JD, Vemulapalli S, Dai D, Matsouaka R, Blackstone E, Edwards F, Masoudi FA, Mack M, Peterson ED, Holmes D, Rumsfeld JS, Tuzcu EM, Grover F. Procedural Experience for Transcatheter Aortic Valve Replacement and Relation to Outcomes: The STS/ACC TVT Registry. J Am Coll Cardiol. 2017 Jul 4;70(1):29-41. doi: 10.1016/j.jacc.2017.04.056. PMID: 28662805.



SENTINEL™ CPS – Procedural Animation

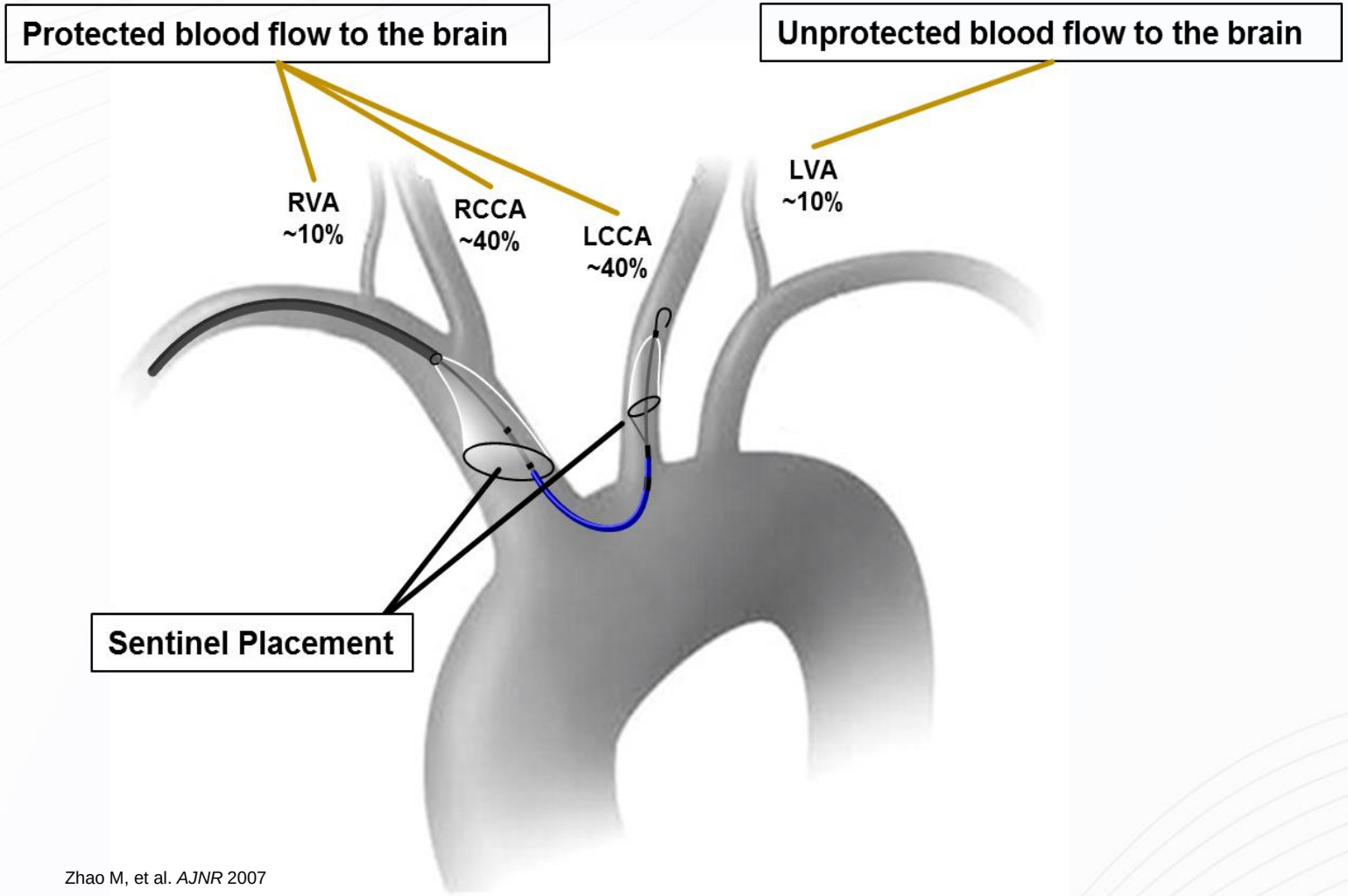
NEWS • Daily News

FDA Clears Sentinel Cerebral Protection Device for Use During TAVR

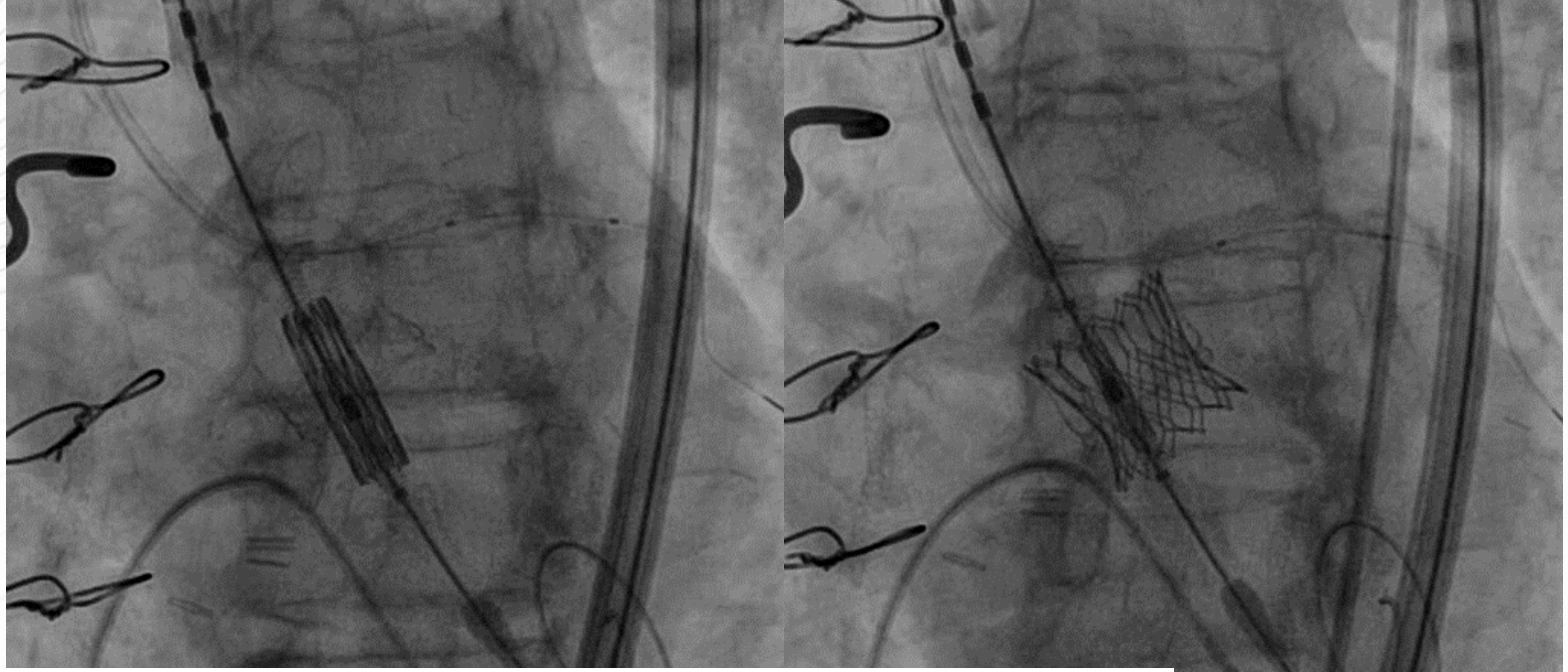
The filter device becomes the first of its kind cleared for use in the United States during transcatheter aortic valve procedures.

by Shelley Wood JUNE 05, 2017

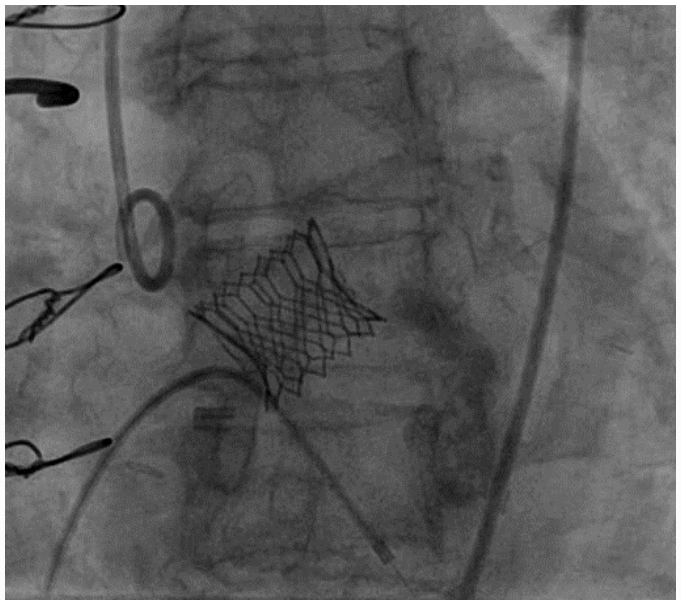
Sentinel Filters >90% of Blood Flow to Brain

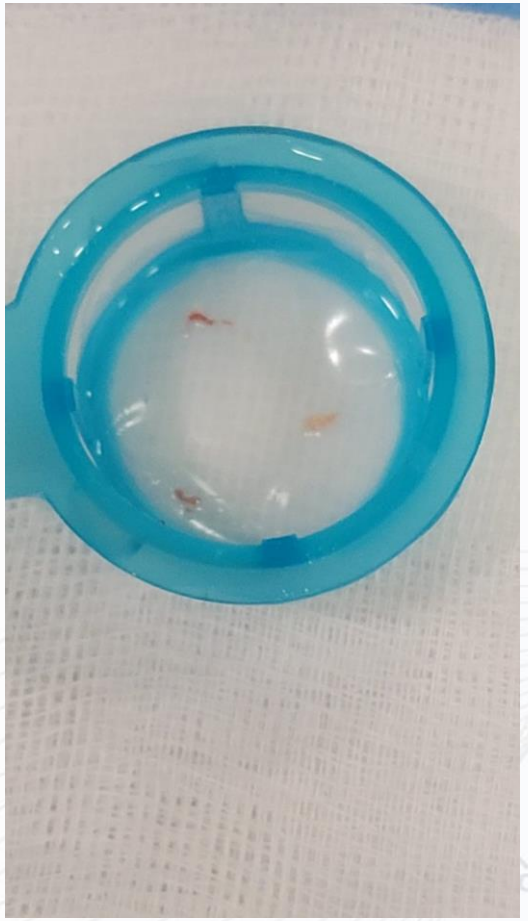


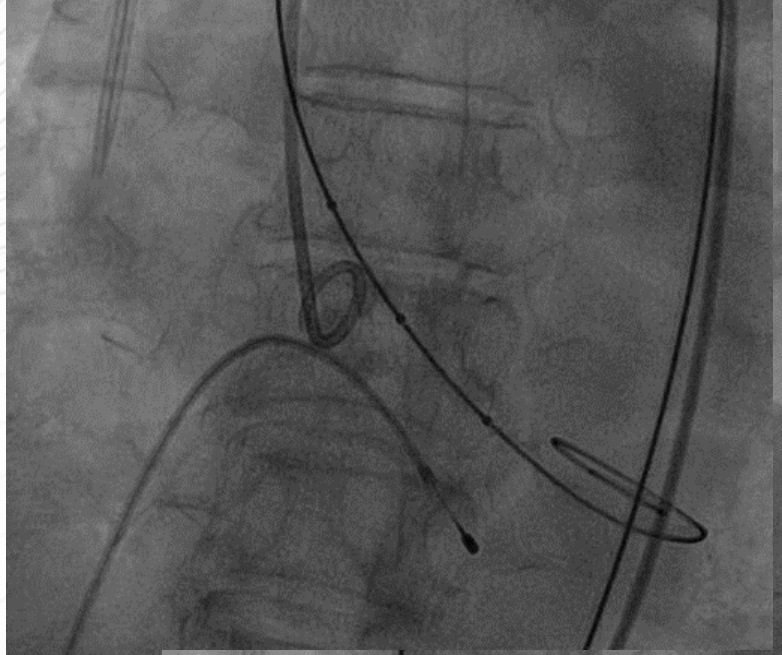
Zhao M, et al. *AJNR* 2007

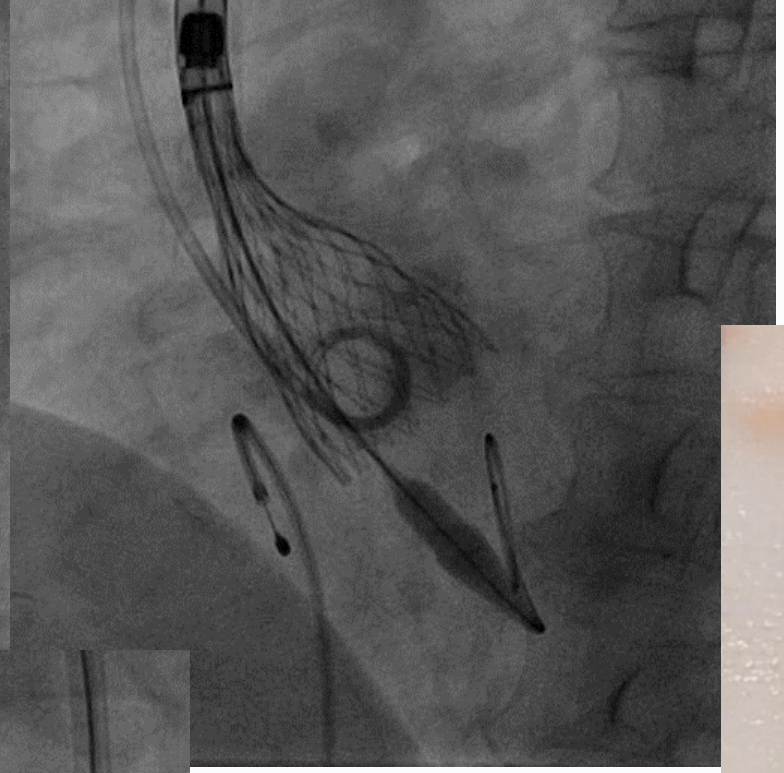


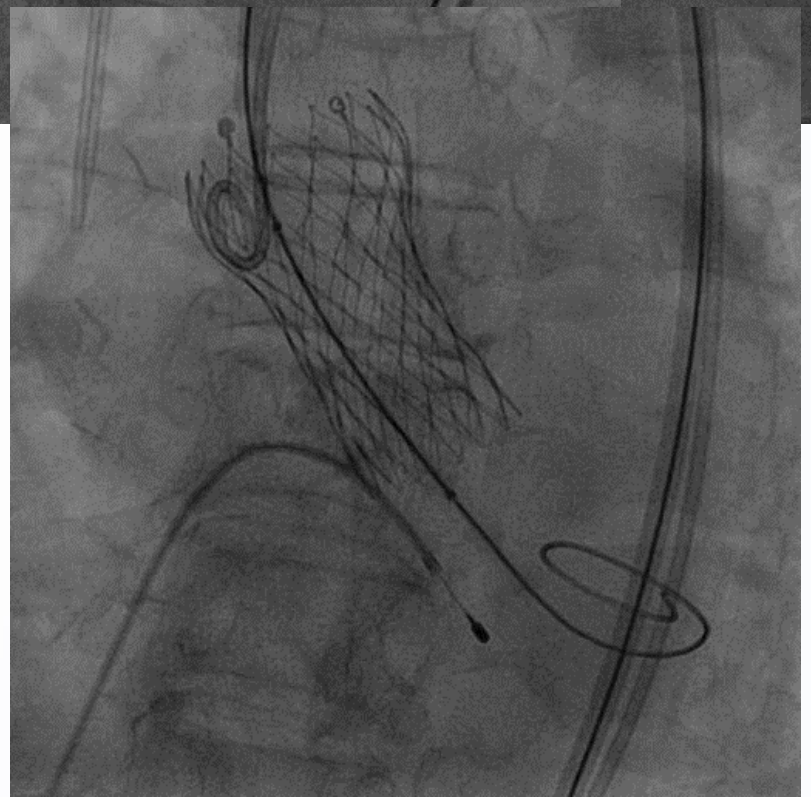
F/70 Severe AS
Valve in Valve TF Edwards SAPIEN3 #20mm in Trifecta #19
Postdilation (+ 2 ml)



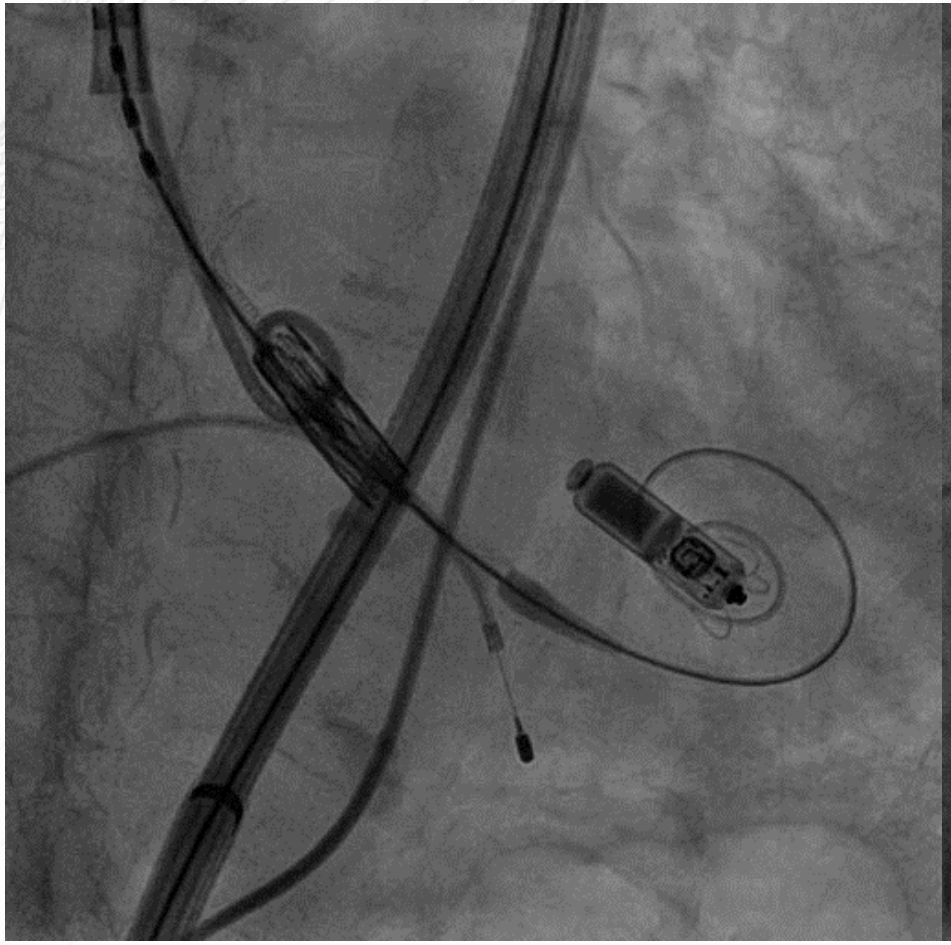


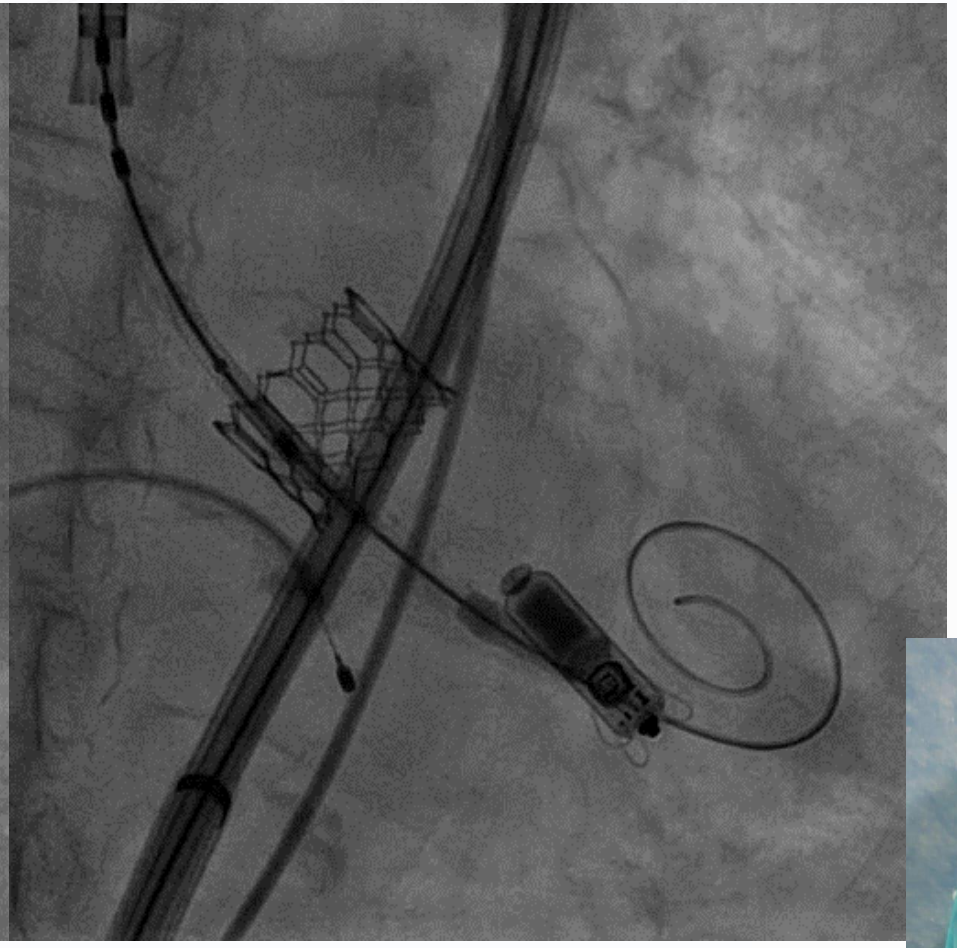


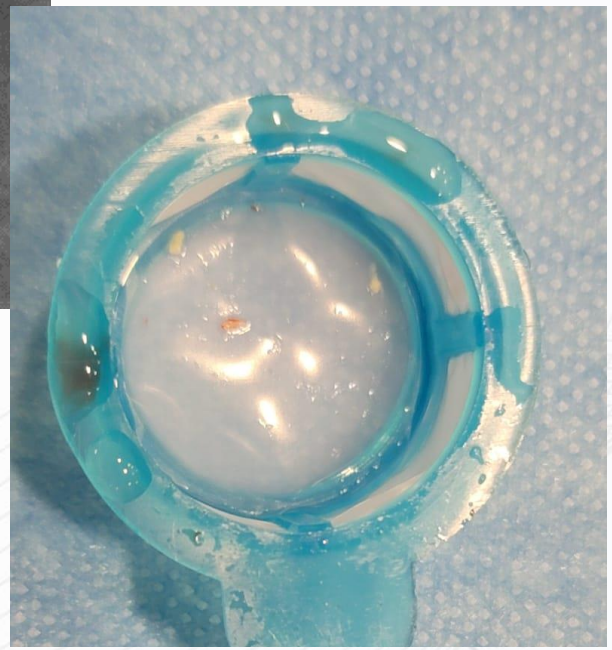




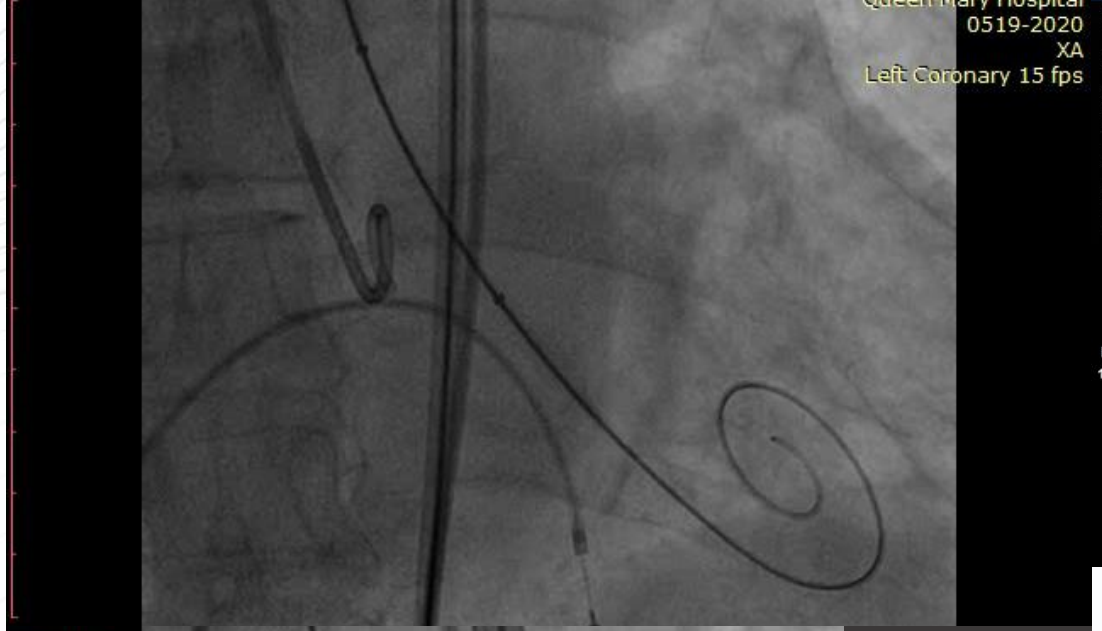
F/80 Severe AS
Predilation NUCLEUS Balloon 20mm X 4cm
TAVI Evolut PRO #29mm – Cusp Overlap (single deploy)
Postdilation TRUE Balloon 20mm X 4cm

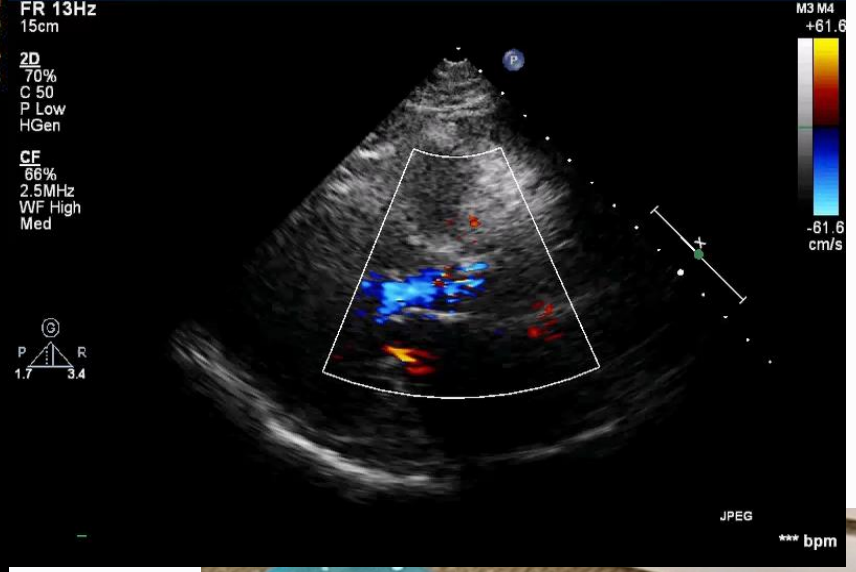


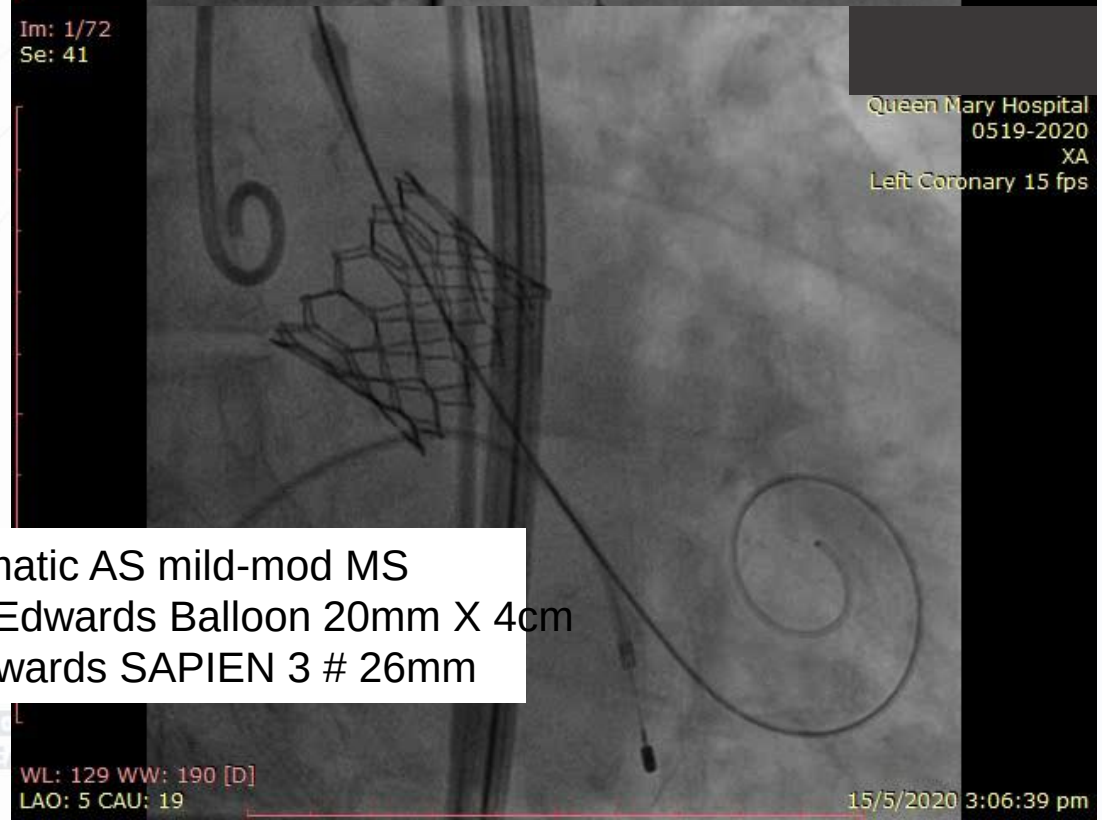




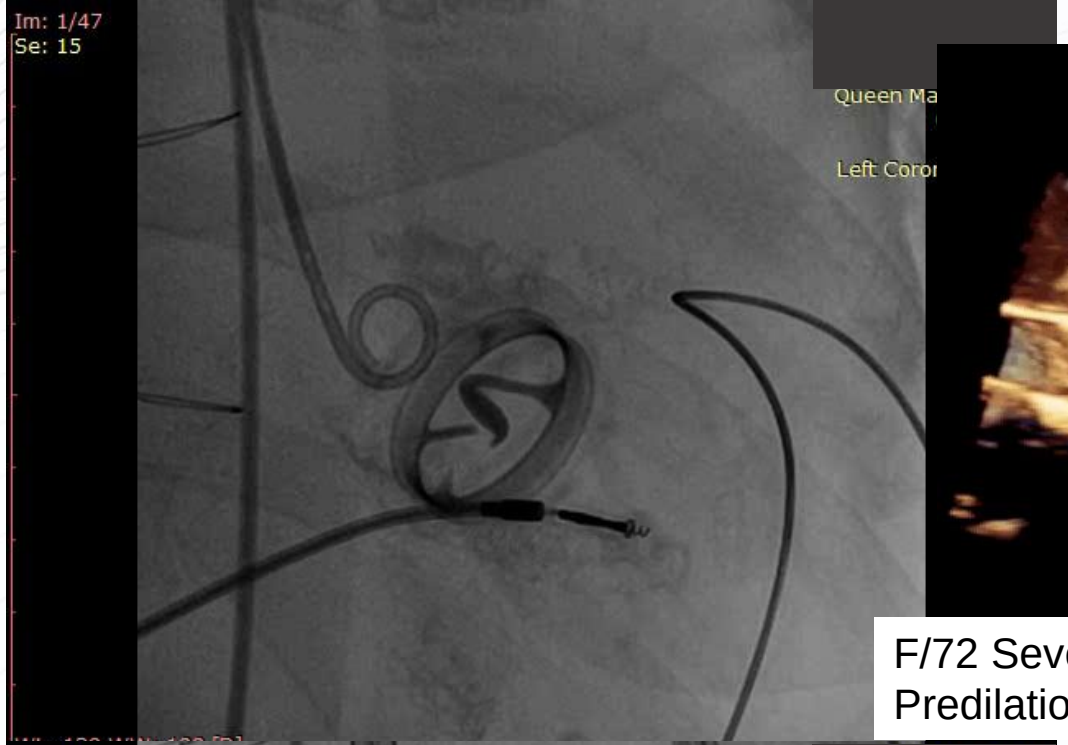
F/94 High degree AV Block
Severe AS Micra Implantation
TF TAVI Edwards SAPIEN3 # 20mm, Postdilation

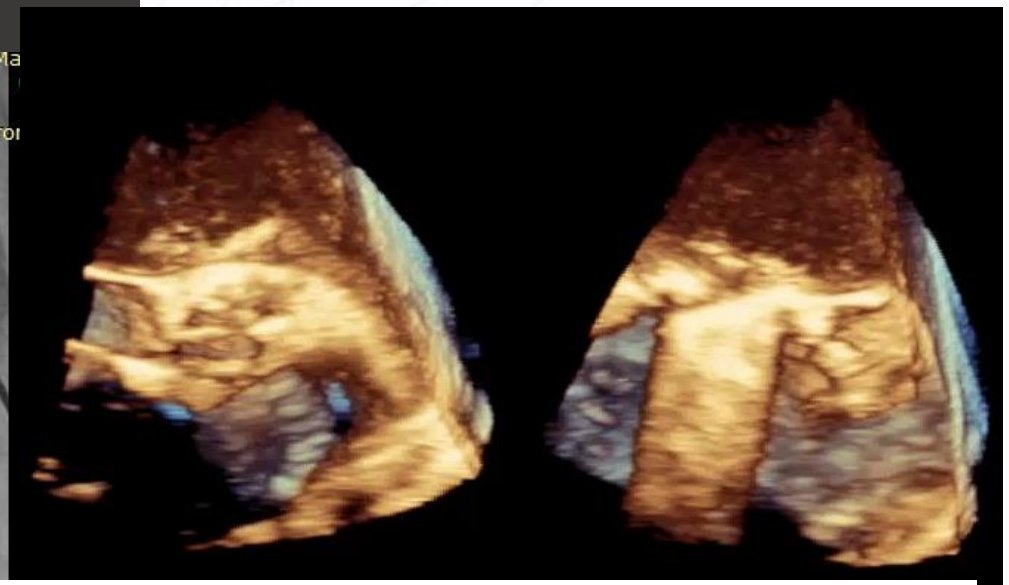




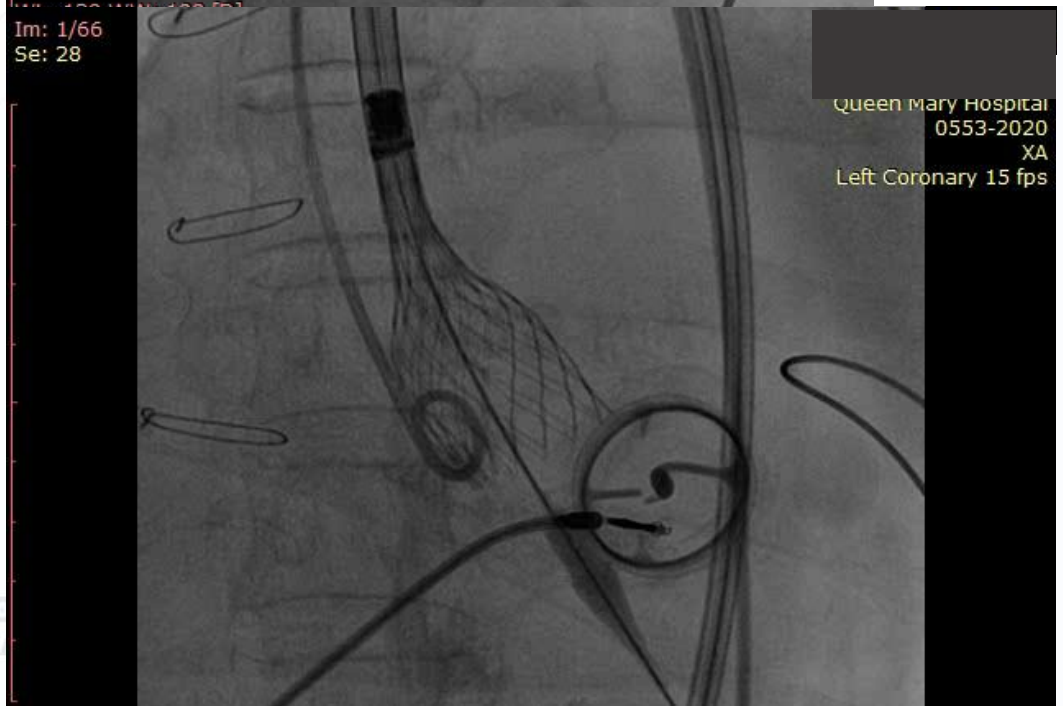


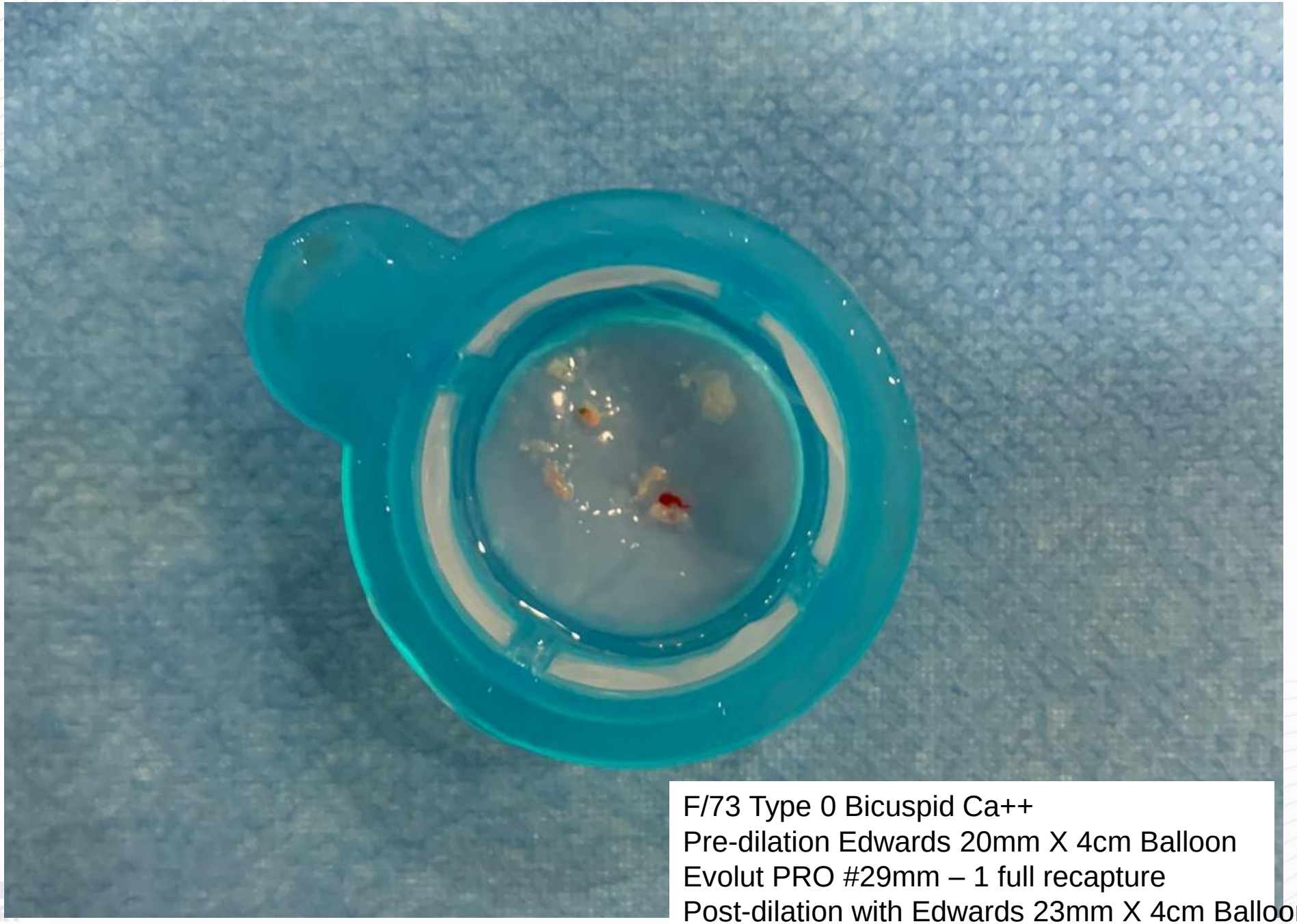
F/75 Rheumatic AS mild-mod MS
Predilation Edwards Balloon 20mm X 4cm
TAVI TF Edwards SAPIEN 3 # 26mm





F/72 Severe AS – Rheumatic/ History of Mechanical [redacted]VR
Predilation, TAVI TF Evolut PRO #26mm (single deploy)



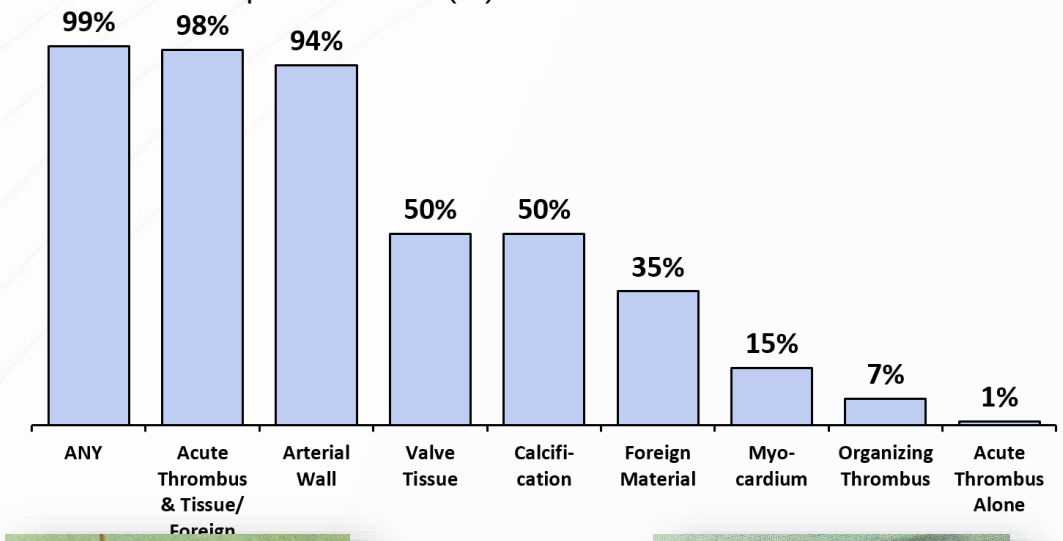


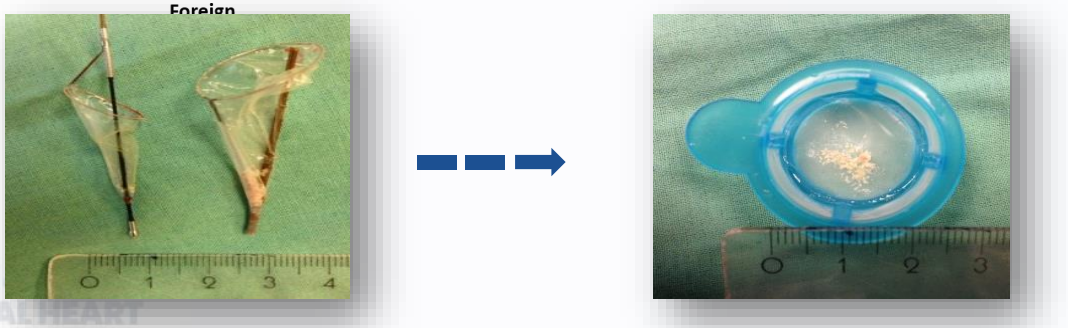
F/73 Type 0 Bicuspid Ca++
Pre-dilation Edwards 20mm X 4cm Balloon
Evolut PRO #29mm – 1 full recapture
Post-dilation with Edwards 23mm X 4cm Balloon

SENTINEL IDE Trial – High Rate of Debris Capture

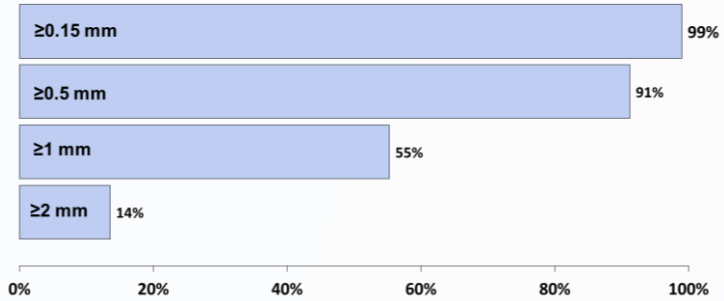
Debris capture in 99% of TAVI patients.

Patients with Captured Debris (%)

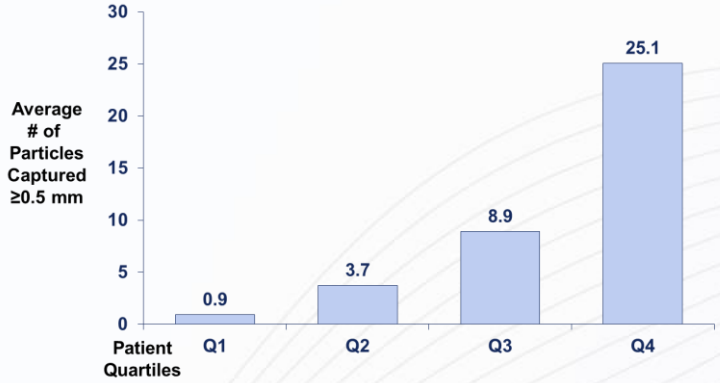




Percent of Patients with at Least One Particle of Given Size



1 in 4 Patients had an average of 25 Particles ≥0.5 mm in Size Captured and Removed



Virmani R, et al. CVPath. SENTINEL IDE Trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

SENTINEL CPS Reduced Cerebral Lesion Volume

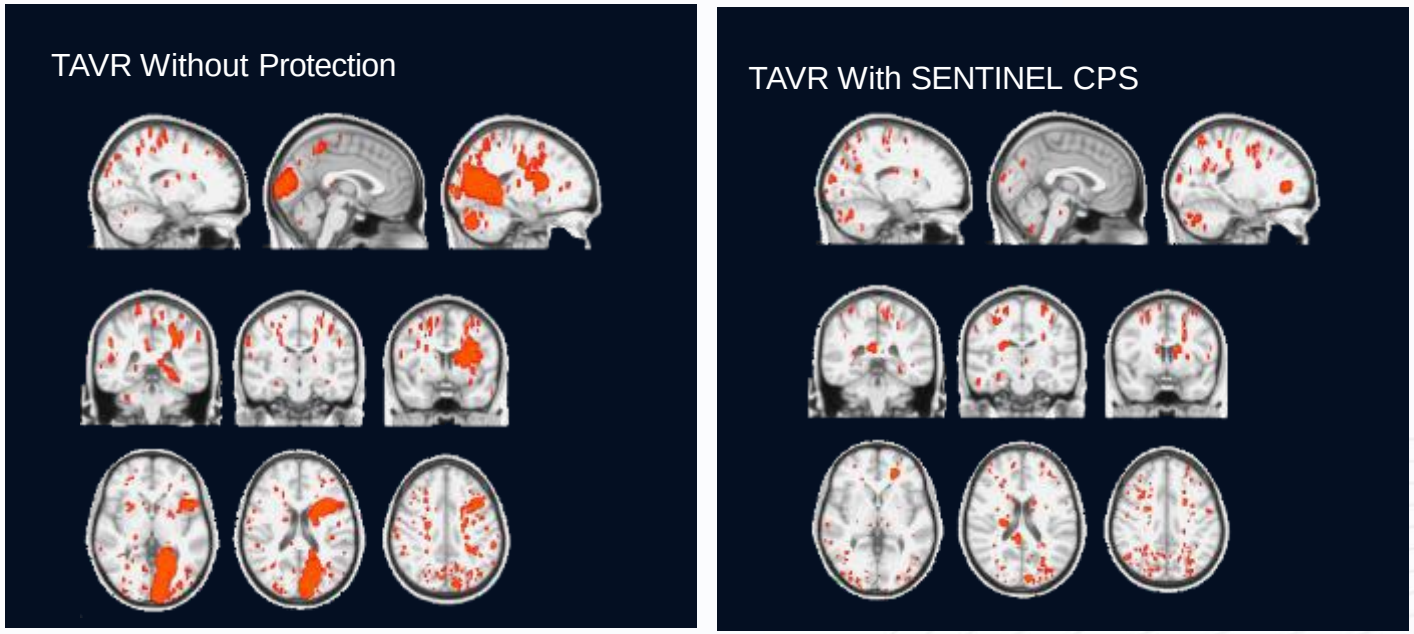
Protection Can Reduce New Lesion Volumes

52% reduction in new lesion volume in whole brain (MISTRAL-C[1])
- 3T MRI assessment at baseline & 2-5 days post-procedure

41% reduction in new lesion volume in whole brain(CLEAN-TAVI[2])
- 3T MRI assessment at baseline, 2 days, 7 days post-procedure

42% reduction* in new lesion volume in whole brain(SENTINEL IDE[3])
- 3T MRI assessment at baseline, 2-7 days post-procedure

The CLEAN-TAVI Randomized Trial Showed Significant Reductions in New Cerebral Lesion Accumulation with SENTINEL CPS Use[2]



Representative slices from each of the orthogonal planes showing new lesions at 2d from each arm of CLEAN-TAVI randomized trial of cerebral embolic protection in TAVI using SENTINEL CPS

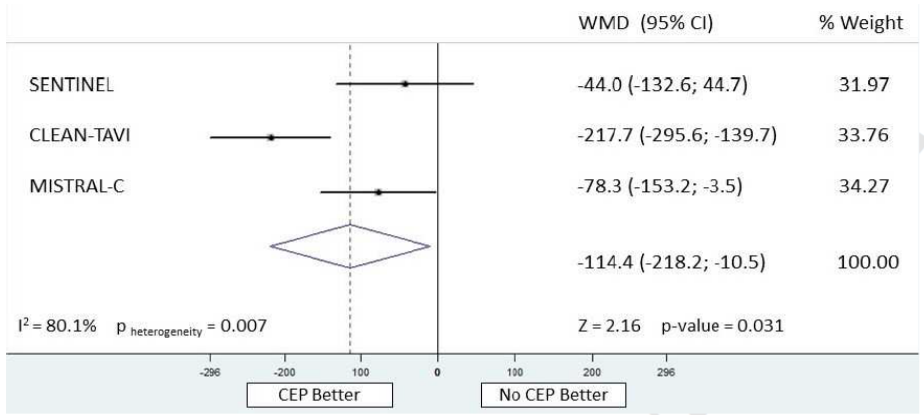
*not statistically significant

1. Van Mieghem N, et al. EuroIntervention 2016;12:499-507 2. Haussig S, et al. Effect of a cerebral protection device on brain lesions following TAVI in patients with severe aortic stenosis. JAMA. 2016;316(6):592-601, 3. Kapadia, et al. JACC. doi: 10.1016/j.jacc.2016.10.023

Combining SENTINEL IDE Trial with CLEAN-TAVI and MISTRAL-C

Shows significant statistical superiority for SENTINEL CPS reducing new lesion volume.

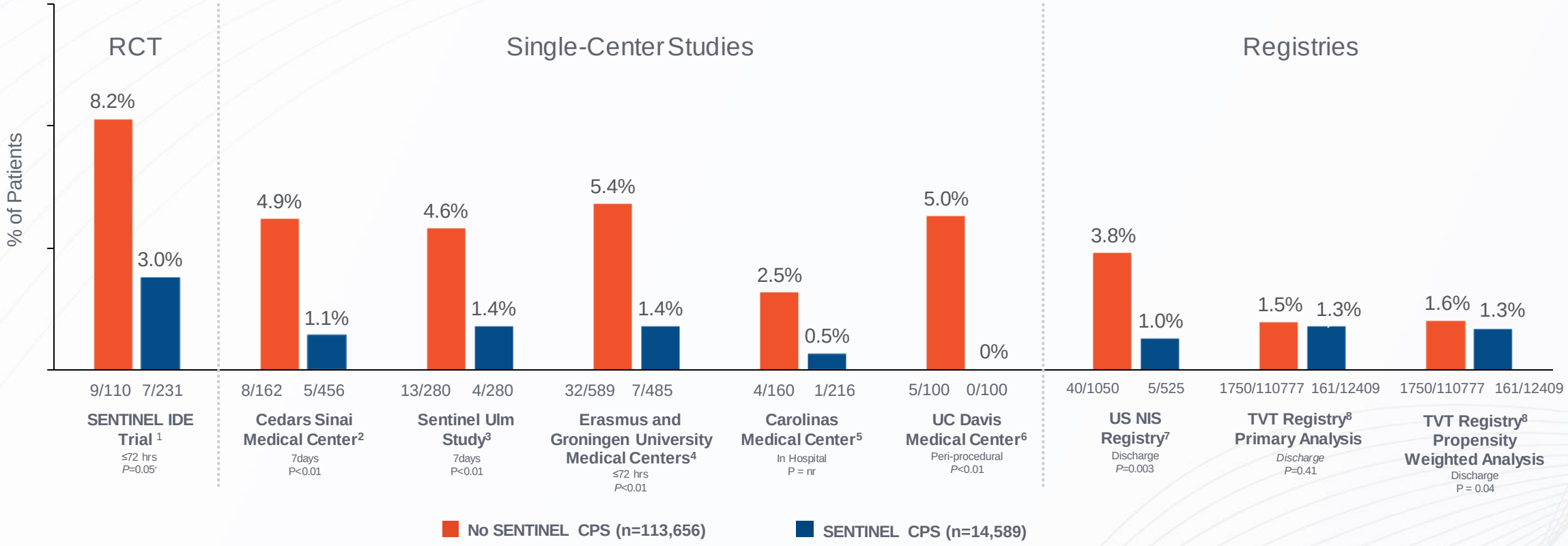
Figure 1: Meta-analysis of randomized controlled trials investigating the Claret cerebral protection filters.



Forest plot shows results for new total lesion volume in patients undergoing TAVR with vs. without cerebral embolic protection (CEP) filters. The weighted mean difference (WMD) among groups equals to -114.4 mm^3 (95% confidence interval [CI], -218.2 mm^3 to -10.5 mm^3), confirming a significant reduction in the analyzed endpoint (p-value 0.031).

Latib A, Pagnesi M, Cerebral embolic protection during transcatheter aortic valve replacement: A disconnect between logic and data?, *JACC* (2016), doi:10.1016/j.jacc.2016.10.036

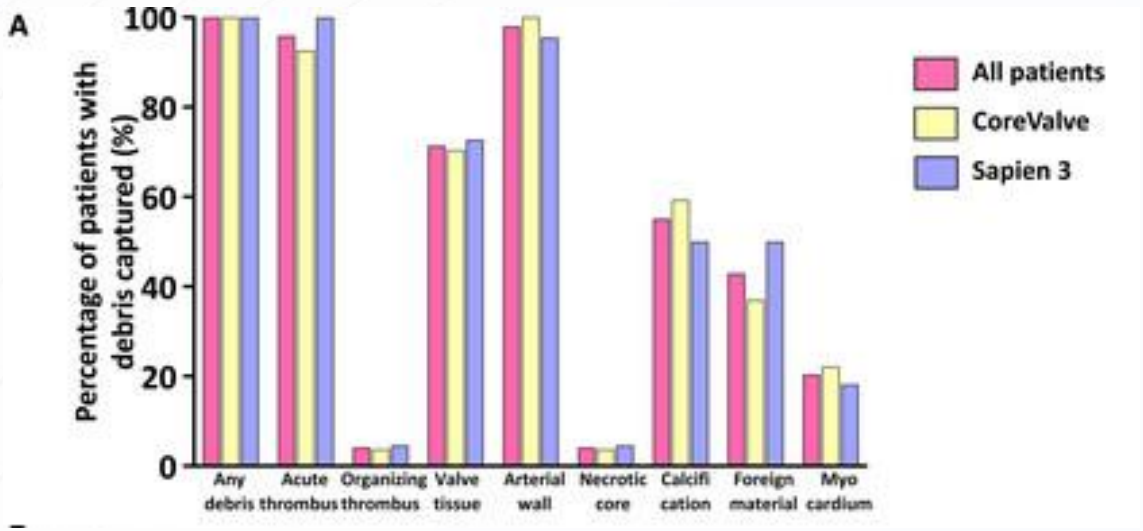
Multiple Studies Suggest SENTINEL CPS Provides 60-80% Stroke Risk Reduction



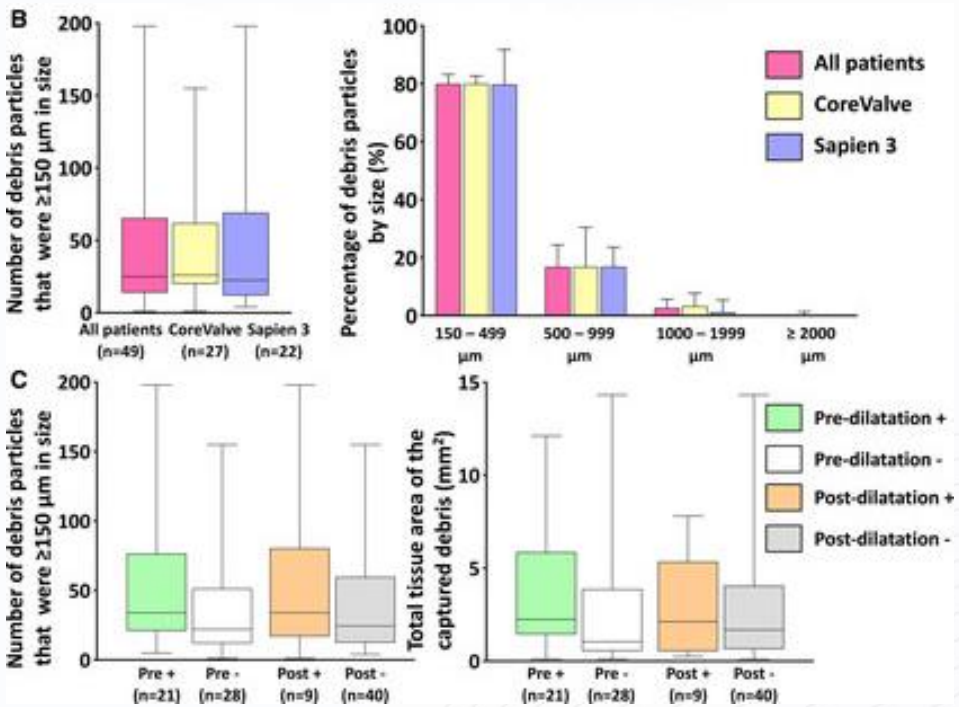
[1]SENTINEL IDE Trial. Data presented at SENTINEL FDA Adv isory Panel, Feb 23, 201; [2]Chakrav arty T, TCT 2018; [3]Seeger J, et al. JACC Cardiov asc Interv . 2017 [4]Van Mieghem N, TVT 2018 (includes TIA); [5] Rinaldi Outcomes with a Sy stematic Application of SENTINEL Cerebral Embolic Protection For TAVR. Data presented at ACC 2021, May 15, 2021. ;[6]Stripe, B. PCR LV 2019; [7]Megaly M. et al Ischemic stroke with cerebral protection sy stem during transcatheter aortic v alv e replacement J Am Coll Cardiol Intv 2020; 13:2149-55 [8]Cohen DJ. Cerebral embolic protection and TAVR outcomes: results from the TVT Registry. Paper presented at: Transcatheter Cardiov ascular Therapeutics Annual Conf erence; October 16, 2020; online. Results from diff erent studies are not directly comparable. Inf ormation prov ided f or educational purposes only.

Use of sentinel in low-intermediate risk patients
The SENTINEL-LIR Study

Debris captured in 100% of the TAVI patients



Larger size particles (≥1000 µm), which can cause significant vessel obstruction, were present in 67% of cases



Characterization of Cerebral Embolic Capture Using the SENTINEL Device During Transcatheter Aortic Valve Implantation in Low to Intermediate-Risk Patients: The SENTINEL-LIR Study
Kawakami et al. - Circulation: Cardiovascular Interventions - 2022

Wolfrum et al. BMC Cardiovascular Disorders (2023) 23:306
https://doi.org/10.1186/s12872-023-03338-0

BMC Cardiovascular Disorders

RESEARCH Open Access

Cerebral embolic protection during transcatheter aortic valve replacement: a systematic review and meta-analysis of propensity score matched and randomized controlled trials using the Sentinel cerebral embolic protection device

Mathias Wolfrum[1,2*†], Immanuel Justus Handerer[2†], Federico Moccetti[1], Alexander Schmeisser[2], Ruediger C. Braun-Dullaeus[2] and Stefan Toggweiler[1]

Abstract

Background The Sentinel cerebral embolic protection device (CEP) aims to reduce the risk of stroke during transcatheter aortic valve replacement (TAVR). We performed a systematic review and meta-analysis of propensity score matched (PSM) and randomized controlled trials (RCT) investigating the effect of the Sentinel CEP to prevent strokes during TAVR.

Methods Eligible trials were searched through PubMed, ISI Web of science databases, Cochrane database, and proceedings of major congresses. Primary outcome was stroke. Secondary outcomes included all-cause mortality, major or life-threatening bleeding, major vascular complications and acute kidney injury at discharge. Fixed and random effect models were used to calculate the pooled risk ratio (RR) with 95% confidence intervals (CI) and absolute risk difference (ARD).

Results A total of 4066 patients from 4 RCTs (3'506 patients) and 1 PSM study (560 patients) were included. Use of Sentinel CEP was successful in 92% of patients and was associated with a significantly lower risk of stroke (RR: 0.67, 95% CI: 0.48–0.95, $p=0.02$. ARD: -1.3%, 95% CI: -2.3 – -0.2, $p=0.02$, number needed to treat (NNT) = 77), and a reduced risk of disabling stroke (RR: 0.33, 95% CI: 0.17–0.65. ARD: -0.9%, 95% CI: -1.5 – -0.3, $p=0.004$, NNT = 111). Use of Sentinel CEP was associated with a lower risk of major or life-threatening bleeding (RR: 0.37, 95% CI: 0.16–0.87, $p=0.02$). Risk for nondisabling stroke (RR: 0.93, 95% CI: 0.62–1.40, $p=0.73$), all-cause mortality (RR: 0.70, 95% CI: 0.35–1.40, $p=0.31$), major vascular complications (RR: 0.74, 95% CI: 0.33–1.67, $p=0.47$) and acute kidney injury (RR: 0.74, 95% CI: 0.37–1.50, $p=0.40$) were similar.

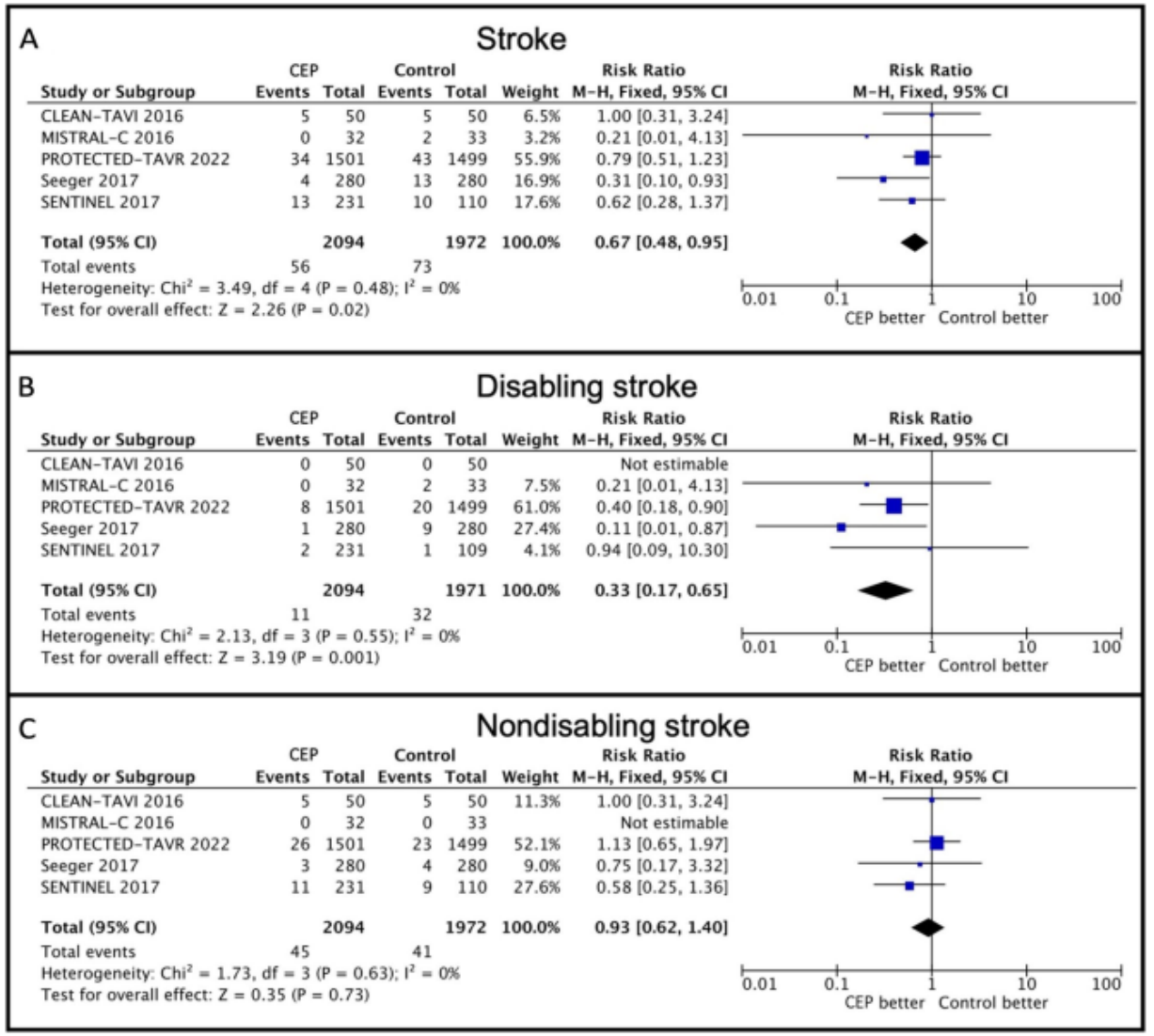


Fig. 2 Stroke in patients undergoing TAVR with versus without Sentinel CEP. Forest plots of individual and summarized risk ratios of all-cause stroke **(A)**, disabling stoke **(B)**, nondisabling stroke **(C)** according to the use of the Sentinel CEP device versus not during TAVR. CI, confidence interval. CLEAN-TAVI, Claret Embolic Protection and TAVI. CEP, cerebral embolic protection. M-H, Mantel–Haenszel. MISTRAL-C, MRI Investigation With Claret. TAVR, transcatheter aortic valve replacement

PROTECTED TAVR Study

Randomized Controlled Trial

The PROTECTED TAVR Trial is an **all-comers study** to prospectively determine if SENTINEL CPS significantly reduces risk of periprocedural stroke (≤ 72 h) after TAVR. All commercially available TAVR devices.

Patients undergoing commercial TF TAVR*, N=3000

Patients of all risk categories eligible

Neurological ‡ exam in all patients pre-procedure

TAVR without Sentinel N=1500	1:1	TAVR with Sentinel N=1500

Neurological ‡ exam in all patients post-procedure

Primary endpoint: Stroke at 72h or Discharge

Adaptive study design with interim analysis at 70% enrollment

The NEW ENGLAND JOURNAL of MEDICINE

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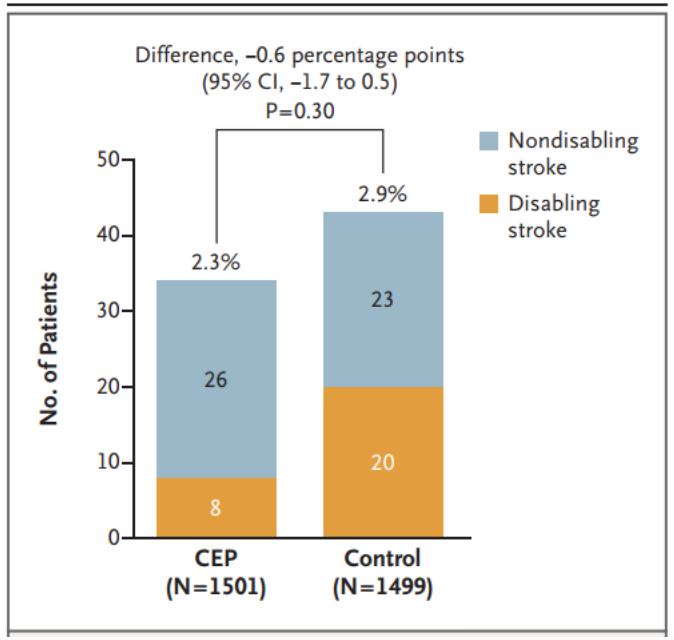
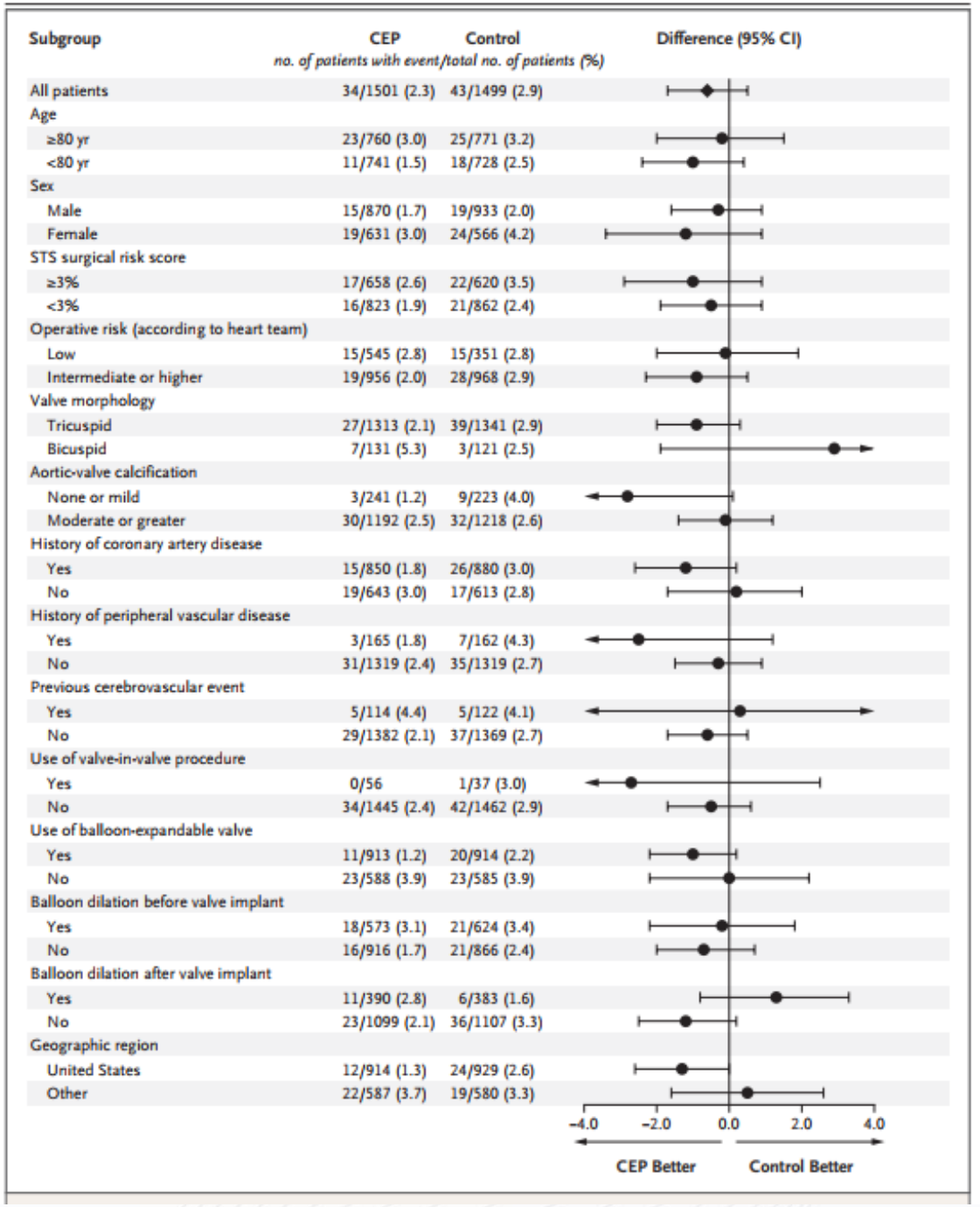
Cerebral Embolic Protection during Transcatheter Aortic-Valve Replacement

Samir R. Kapadia, M.D., Raj Makkar, M.D., Martin Leon, M.D., Mohamed Abdel-Wahab, M.D., Thomas Waggoner, D.O., Steffen Massberg, M.D., Wolfgang Rottbauer, M.D., Ph.D., Samuel Horr, M.D., Lars Sondergaard, M.D., Juhana Karha, M.D., Robert Gooley, M.B., B.S., Ph.D., Lowell Satler, M.D., Robert C. Stoler, M.D., Steven R. Messé, M.D., Suzanne J. Baron, M.D., Julia Seeger, M.D., Susheel Kodali, M.D., Amar Krishnaswamy, M.D., Vinod H. Thourani, M.D., Katherine Harrington, M.D., Stuart Pocock, Ph.D., Rodrigo Modolo, M.D., Ph.D., Dominic J. Allocco, M.D., Ian T. Meredith, M.D., Ph.D., and Axel Linke, M.D., for the PROTECTED TAVR Investigators*





Protected TAVR Trial

Disabling Stroke

CEP – 8/1501 (0.5%)

Control – 20/1499 (1.3%)

Significant reduction NNT 125

BACKGROUND

Transcatheter aortic-valve replacement (TAVR) for the treatment of aortic stenosis can lead to embolization of debris. Capture of debris by devices that provide cerebral embolic protection (CEP) may reduce the risk of stroke.

METHODS

We randomly assigned patients with aortic stenosis in a 1:1 ratio to undergo transfemoral TAVR with CEP (CEP group) or without CEP (control group). The primary end point was stroke within 72 hours after TAVR or before discharge (whichever came first) in the intention-to-treat population. Disabling stroke, death, transient ischemic attack, delirium, major or minor vascular complications at the CEP access site, and acute kidney injury were also assessed. A neurology professional examined all the patients at baseline and after TAVR.

RESULTS

A total of 3000 patients across North America, Europe, and Australia underwent randomization; 1501 were assigned to the CEP group and 1499 to the control group. A CEP device was successfully deployed in 1406 of the 1489 patients (94.4%) in whom an attempt was made. The incidence of stroke within 72 hours after TAVR or before discharge did not differ significantly between the CEP group and the control group (2.3% vs. 2.9%; difference, −0.6 percentage points; 95% confidence interval, −1.7 to 0.5; P=0.30). Disabling stroke occurred in 0.5% of the patients in the CEP group and in 1.3% of those in the control group. There were no substantial differences between the CEP group and the control group in the percentage of patients who died (0.5% vs. 0.3%); had a stroke, a transient ischemic attack, or delirium (3.1% vs. 3.7%); or had acute kidney injury (0.5% vs. 0.5%). One patient (0.1%) had a vascular complication at the CEP access site.

CONCLUSIONS

Among patients with aortic stenosis undergoing transfemoral TAVR, the use of CEP did not have a significant effect on the incidence of periprocedural stroke, but on the basis of the 95% confidence interval around this outcome, the results may not rule out a benefit of CEP during TAVR. (Funded by Boston Scientific; PROTECTED TAVR ClinicalTrials.gov number, NCT04149535.)

The authors' affiliations are listed in the Appendix. Dr. Kapadia can be contacted at kapadis@ccf.org or at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., J2-3, Cleveland, OH 44195.

*A full list of the PROTECTED TAVR investigators is provided in the Supplementary Appendix, available at NEJM.org.

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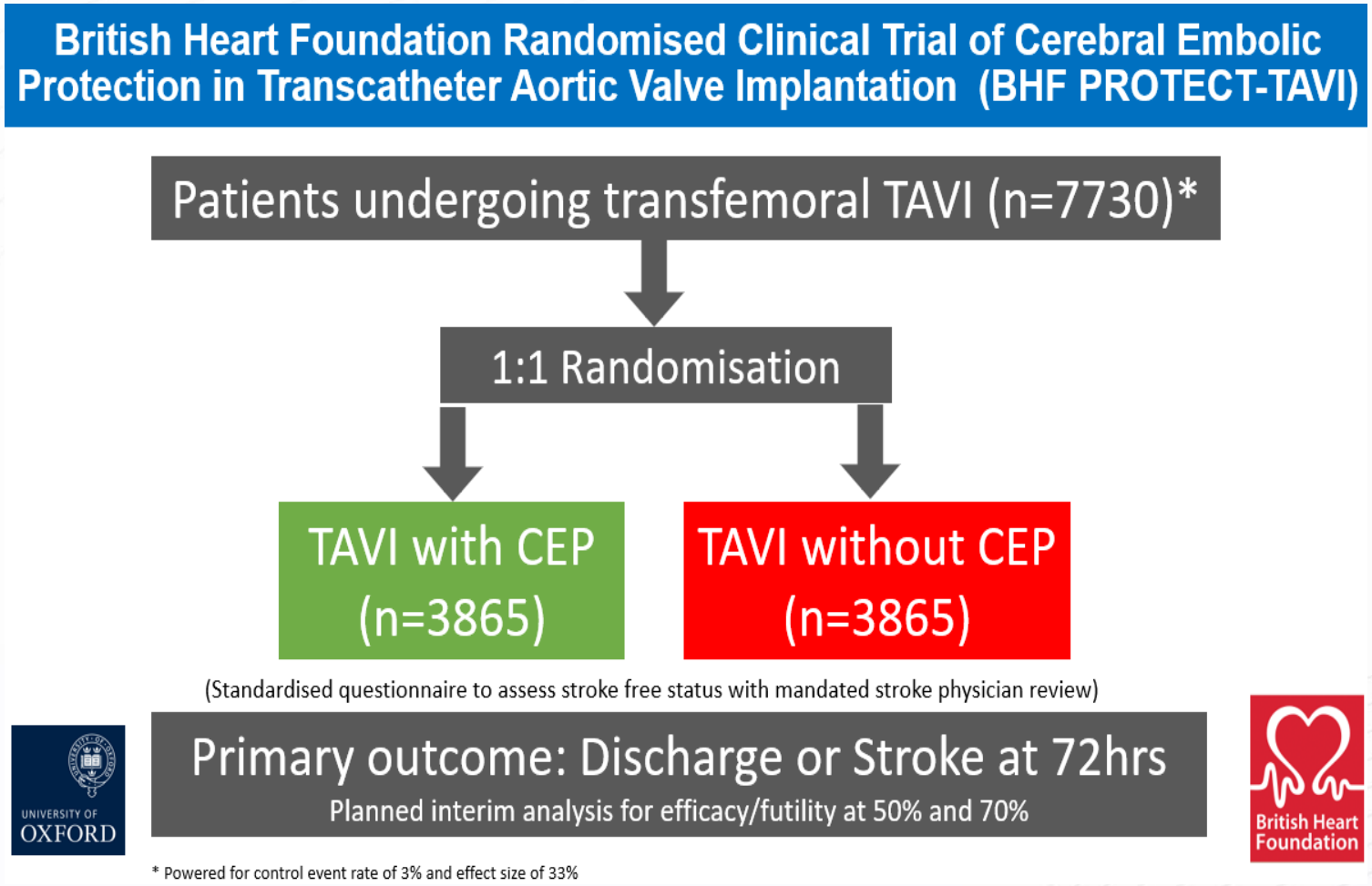
BHF PROTECT-TAVI

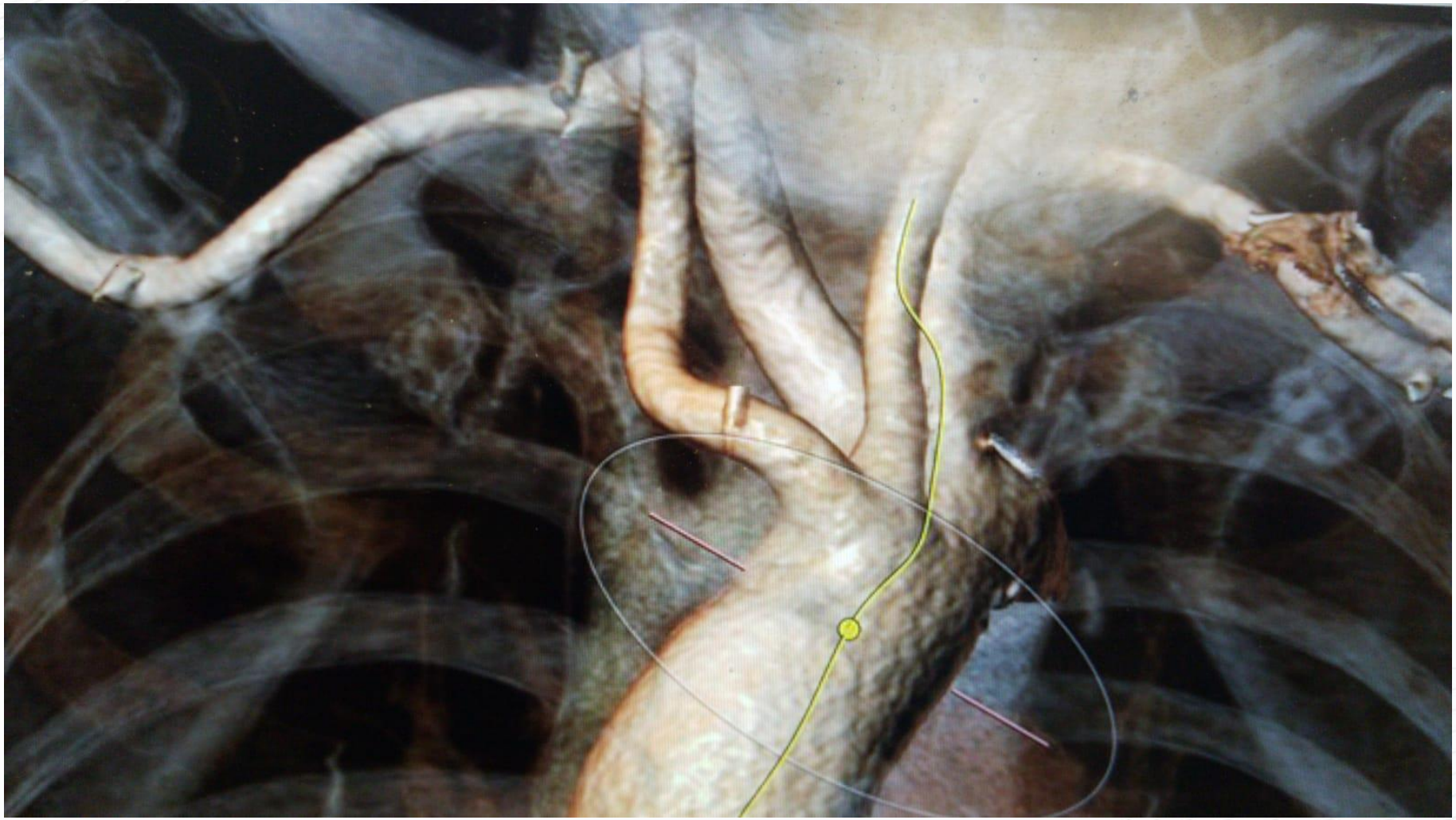
Chief Investigator: Professor Rajesh Kharbanda

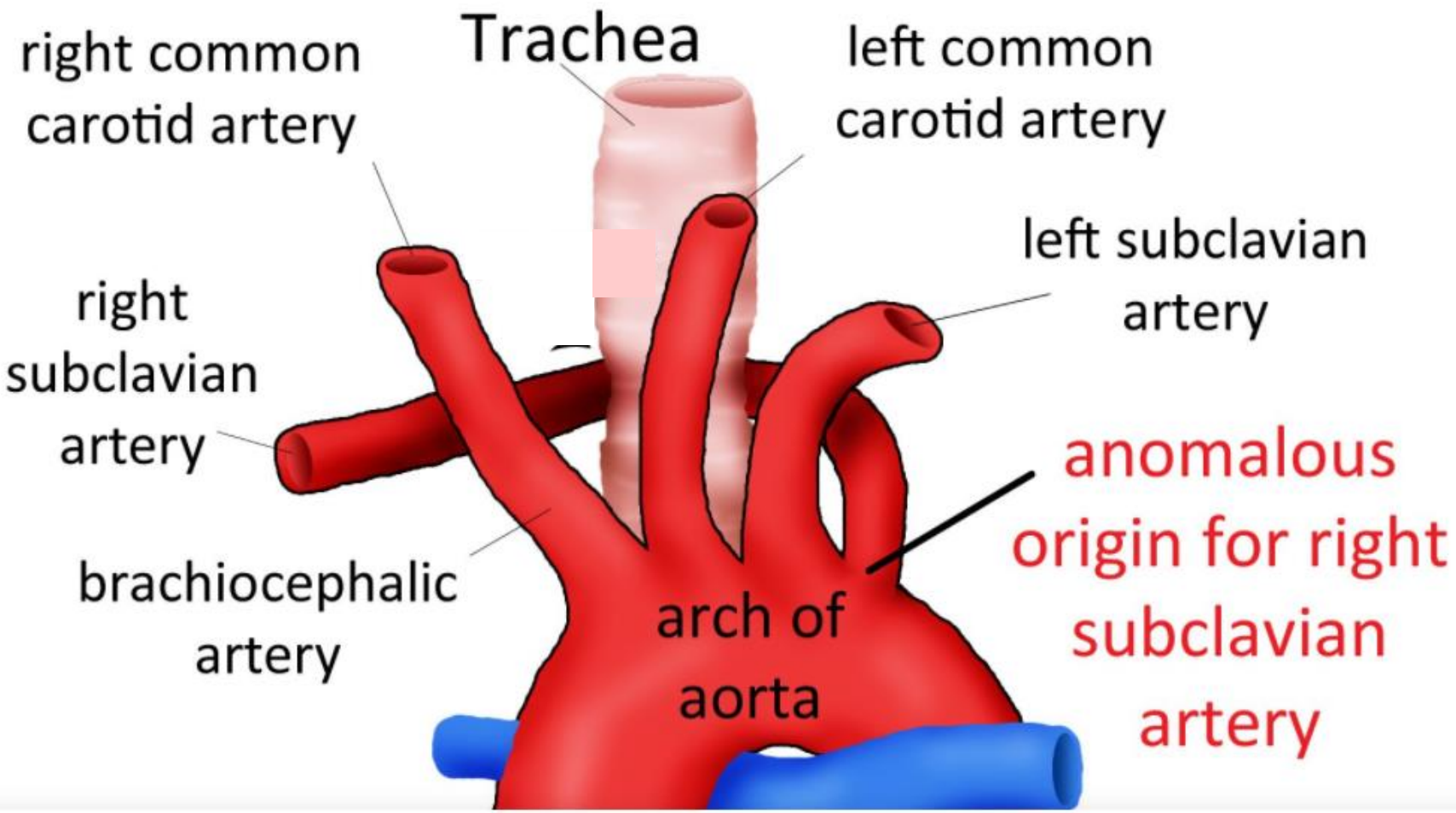


SENTINEL PROTECTION: A Global Prospective Meta-Analysis of the PROTECTED TAVR and BHF PROTECT-TAVI Studies

Principal Investigators: Samir Kapadia, Raj Kharbanda

- **Context:** P-TAVR and BHF-P-TAVI are the only randomized and powered studies to date designed to detect reduction in clinical stroke using CEP
- **Main outcome:** Clinical stroke at 72 hours post-TAVI or hospital discharge (whichever first).
- **Participants/population:** Patients from PROTECTED TAVR and BHF PROTECT-TAVI
- **Additional outcomes**
  - All-cause mortality (cardiovascular and non-cardiovascular)
  - 30-Day Stroke Mortality
  - Stroke severity (disabling and non-disabling)
  - Stroke disability composite of all-cause mortality and all stroke
  - Neurocognitive outcome
  - Length of stay
  - Discharge destination
- **Timing:** Analysis to be conducted following completion BHF PROTECT-TAVI (~July 2026)

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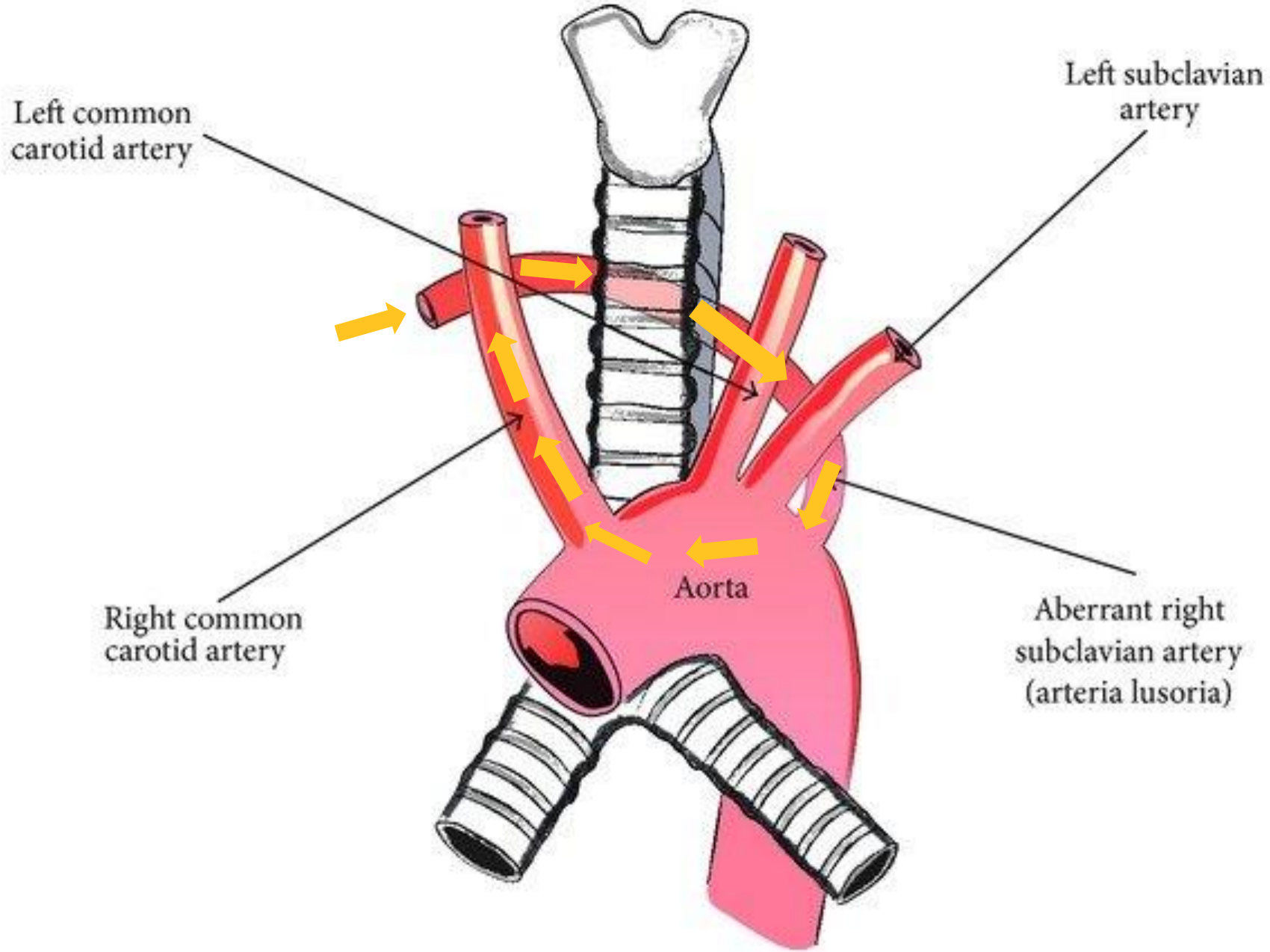
Trachea
left common carotid artery
left subclavian artery
right subclavian artery
anomalous origin for right subclavian artery
brachiocephalic artery
arch of aorta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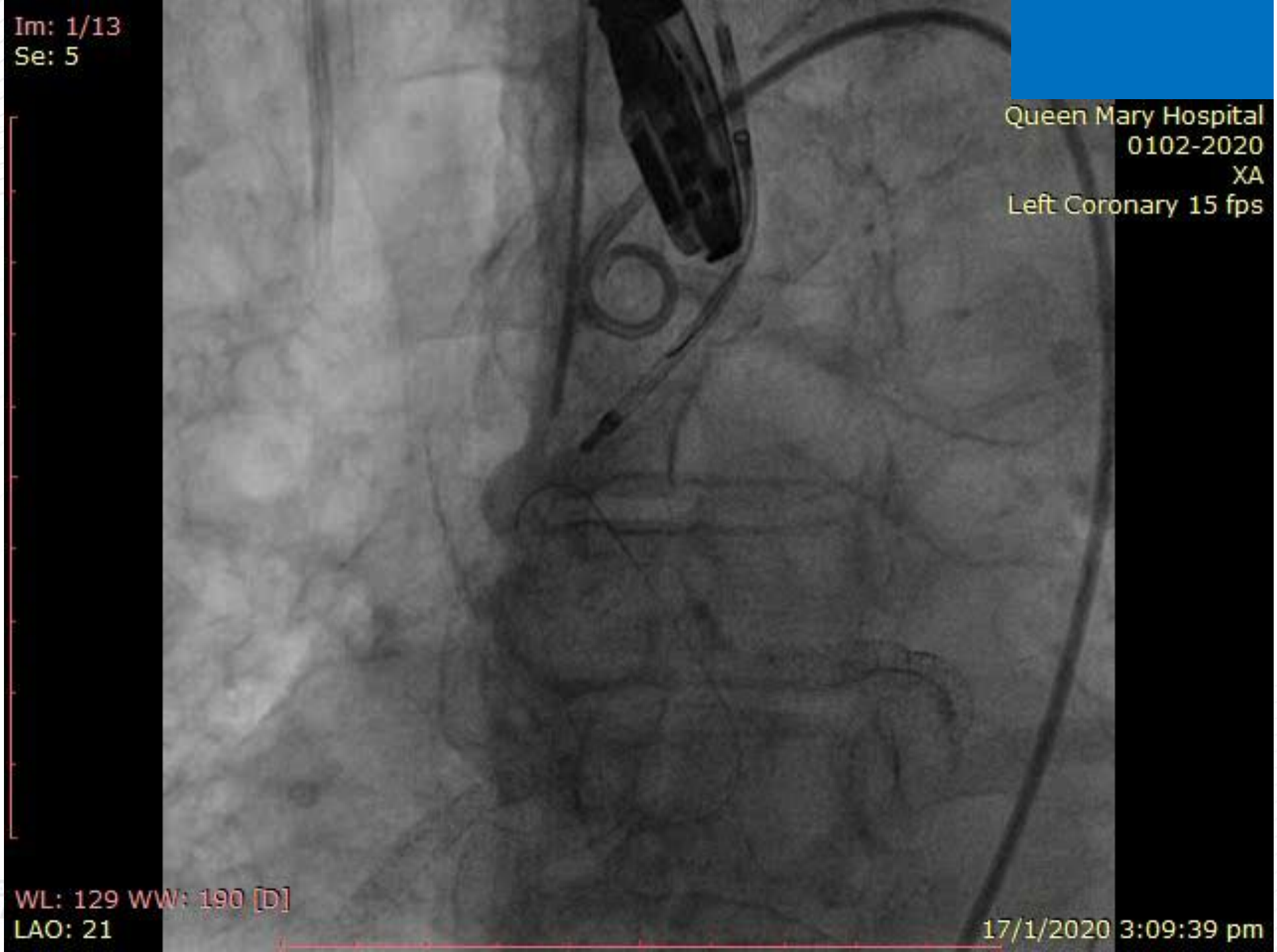
Left subclavian artery
Aorta
Right common carotid artery
Aberrant right subclavian artery (arteria lusoria)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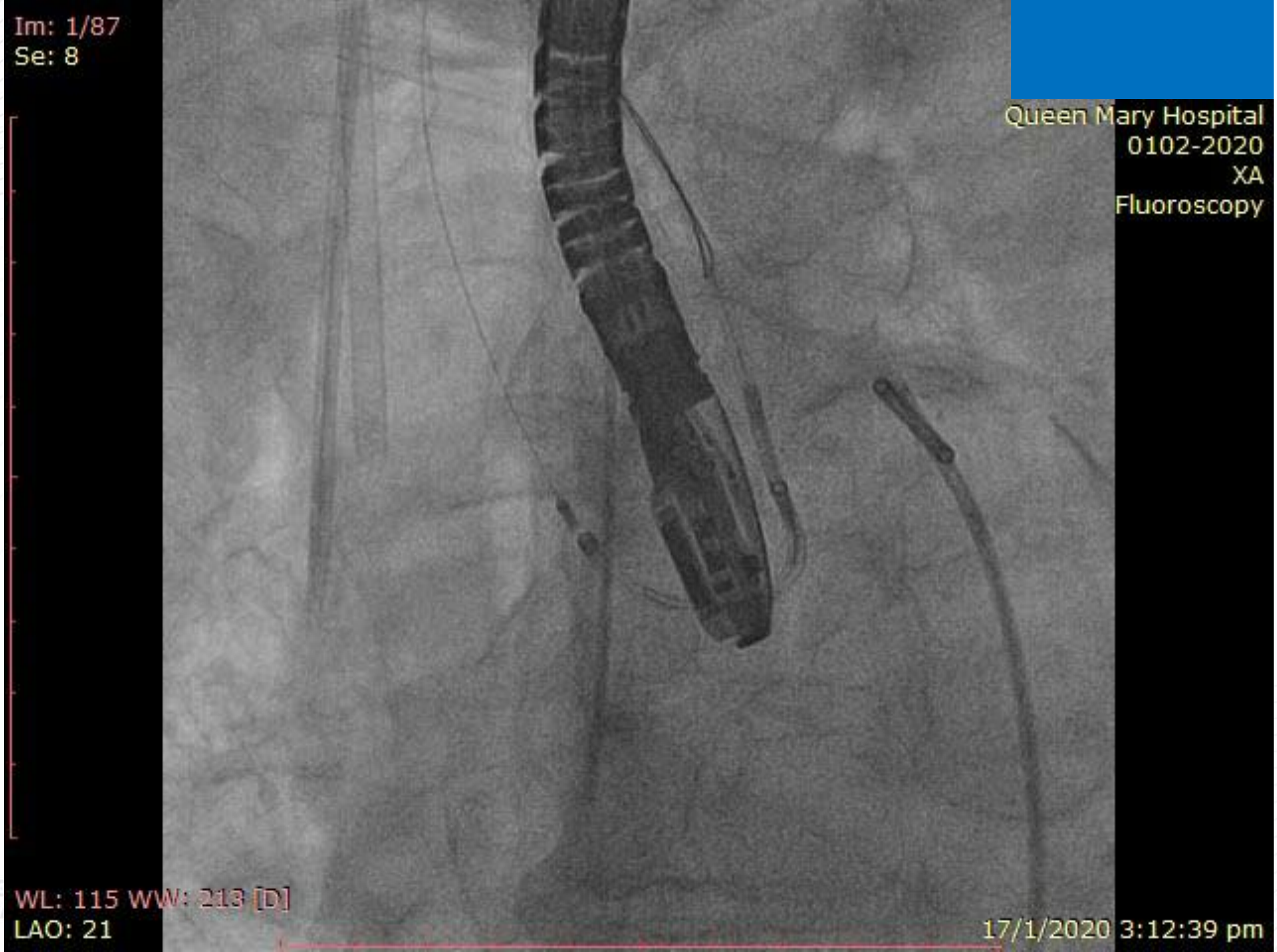
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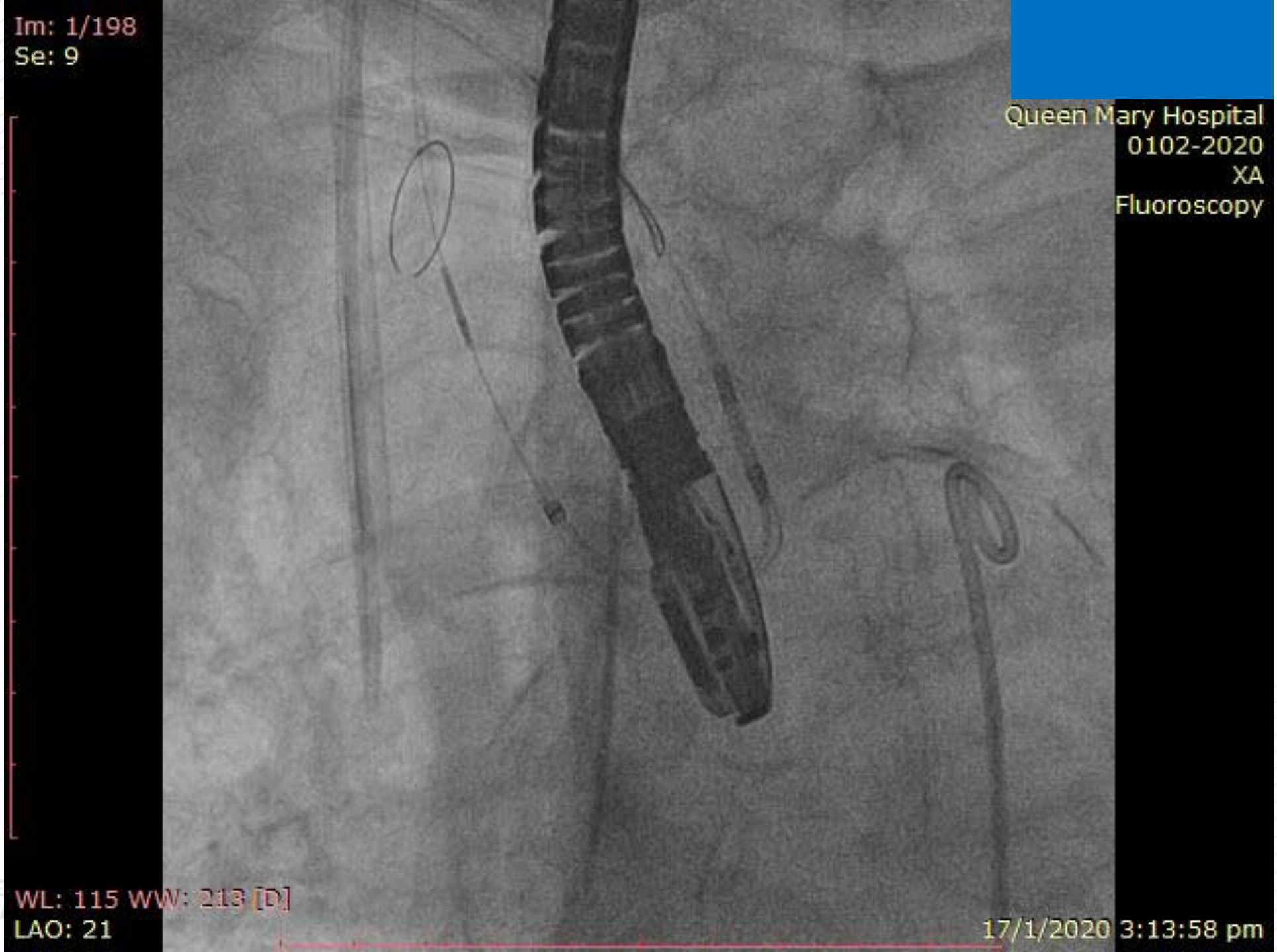
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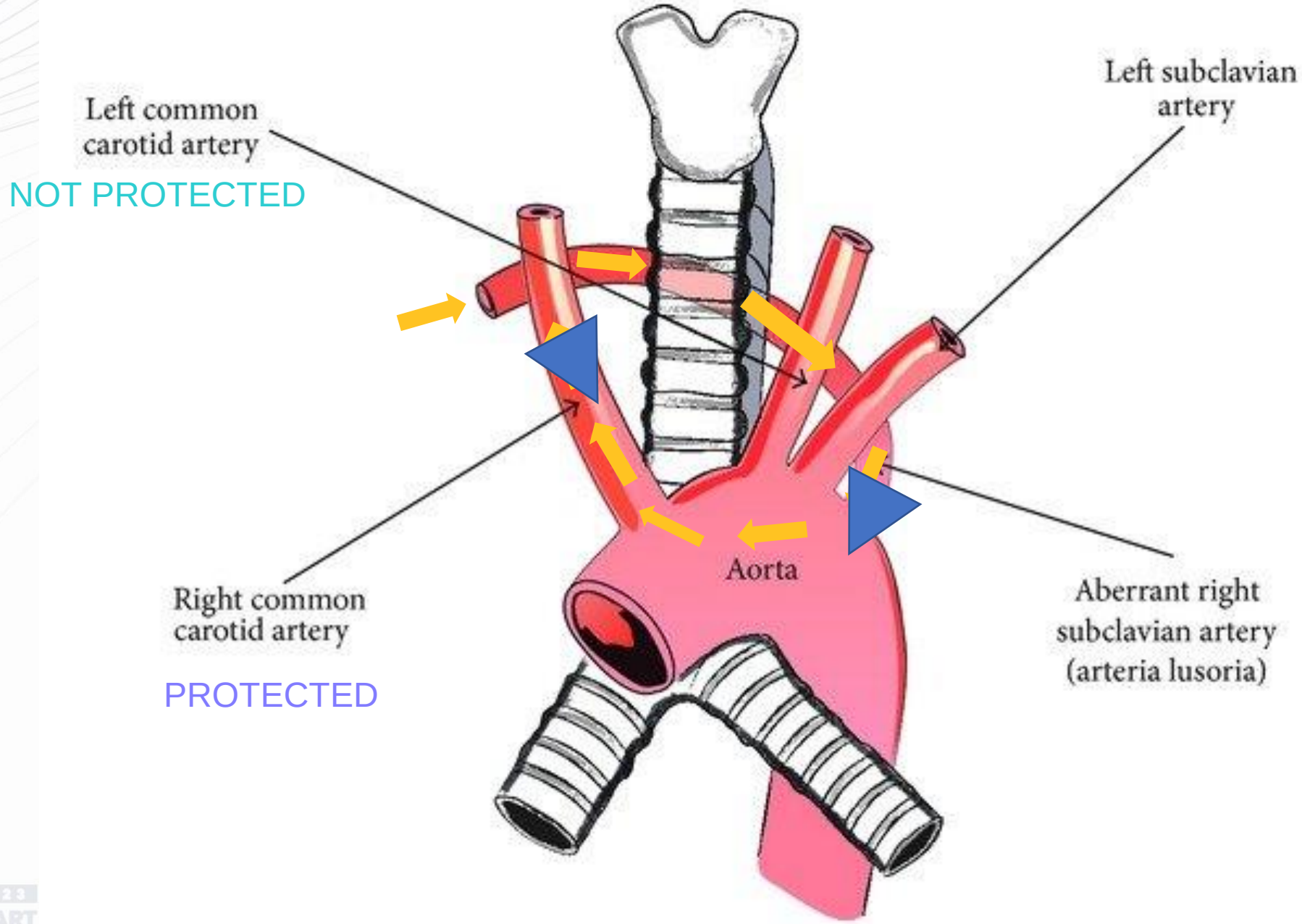
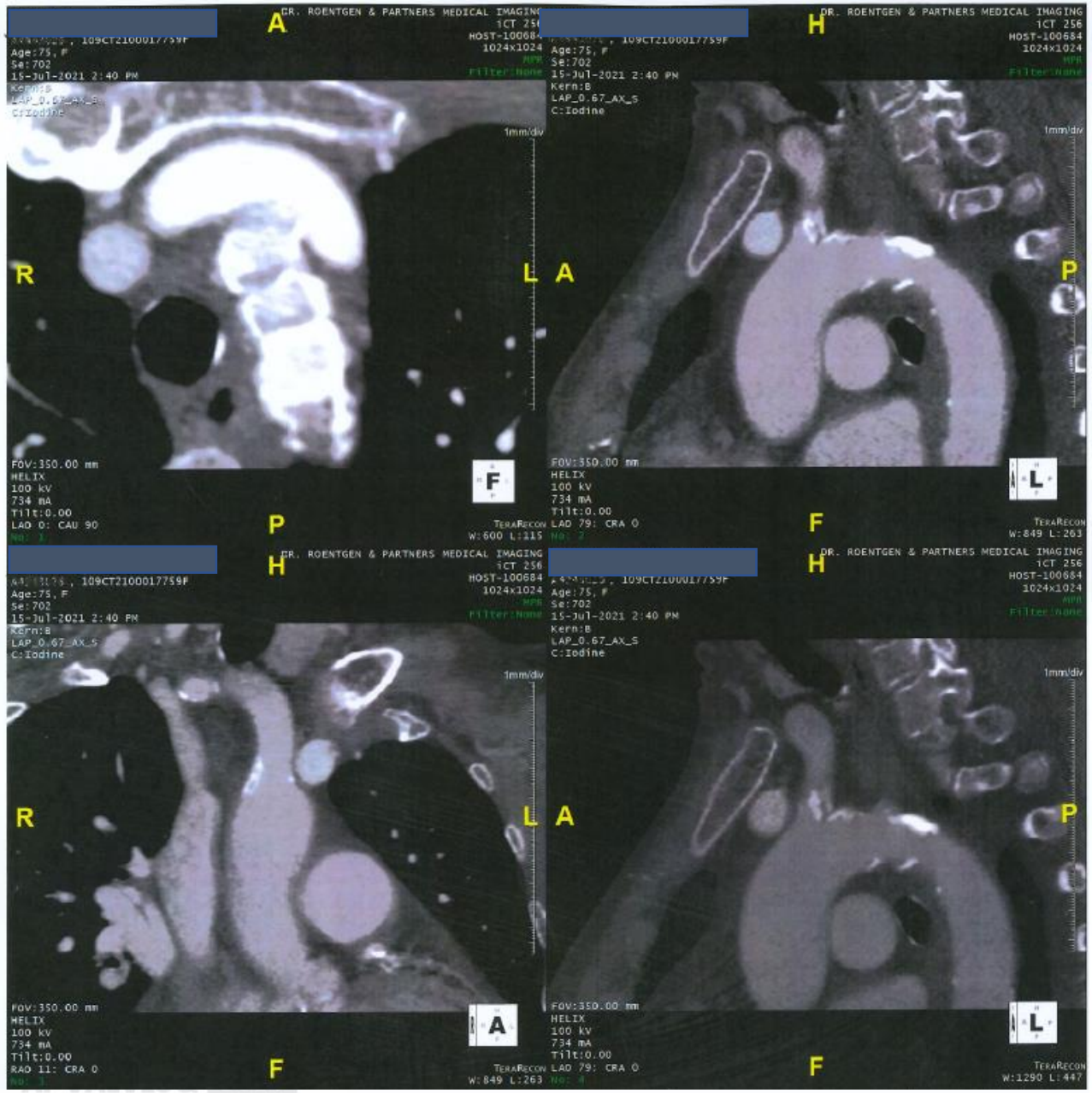

Left common carotid artery
NOT PROTECTED
Left subclavian artery
Aorta
Right common carotid artery
PROTECTED
Aberrant right subclavian artery (arteria lusoria)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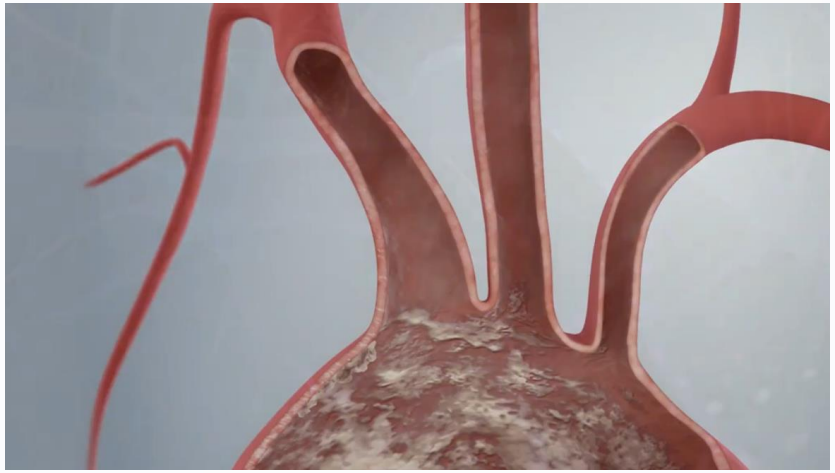

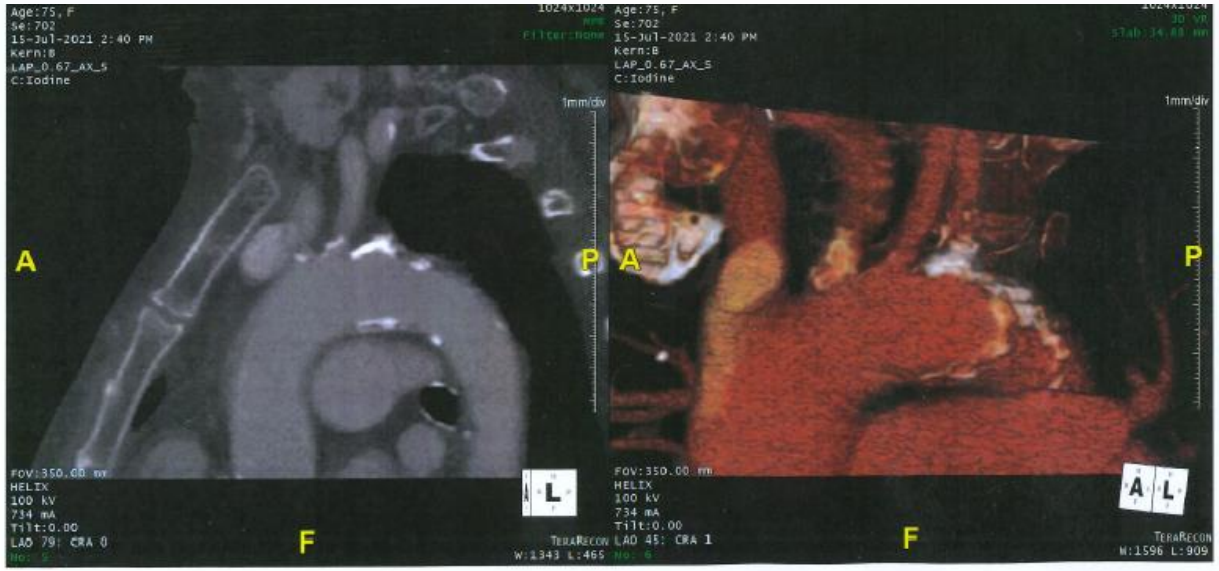
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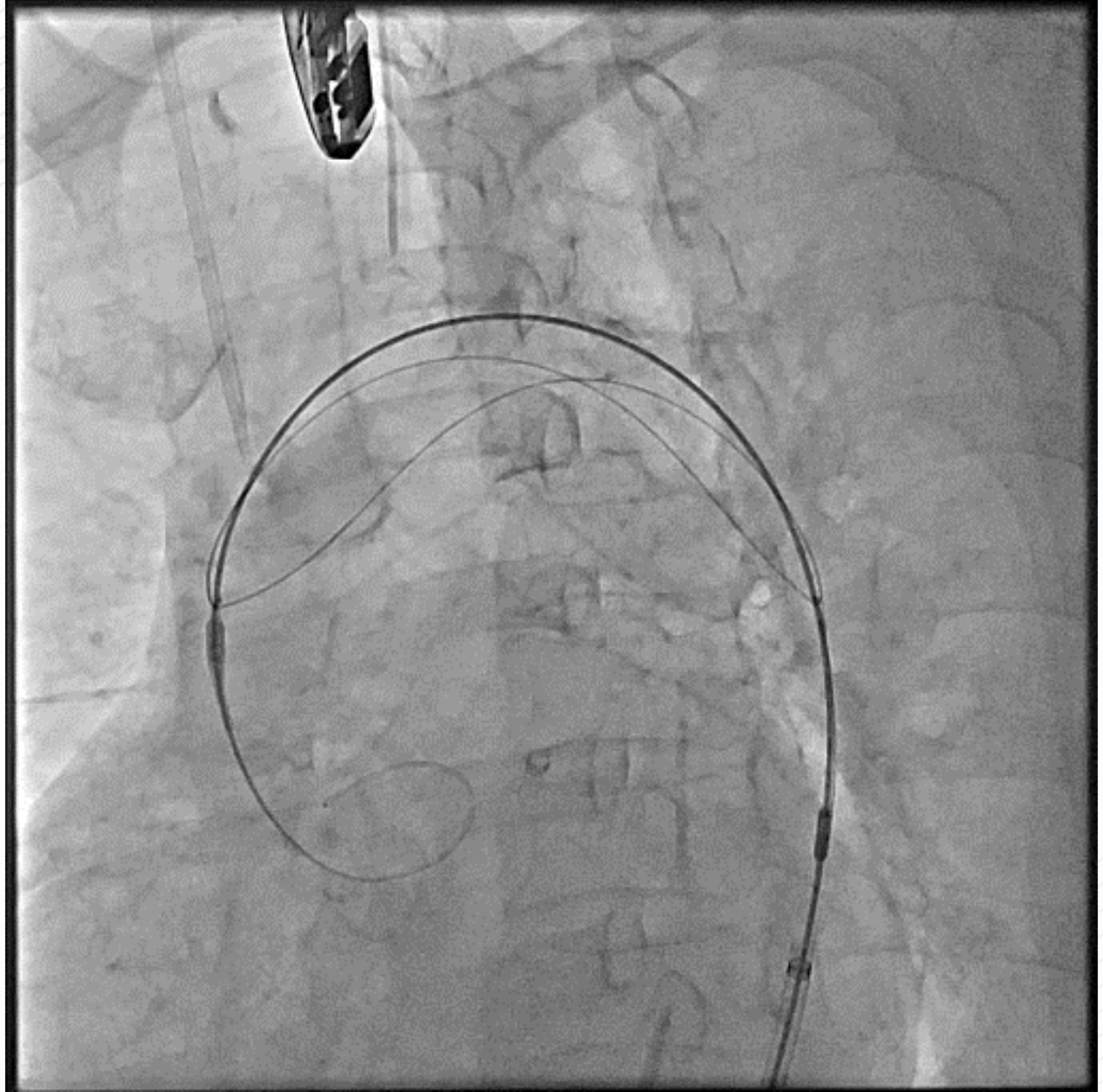

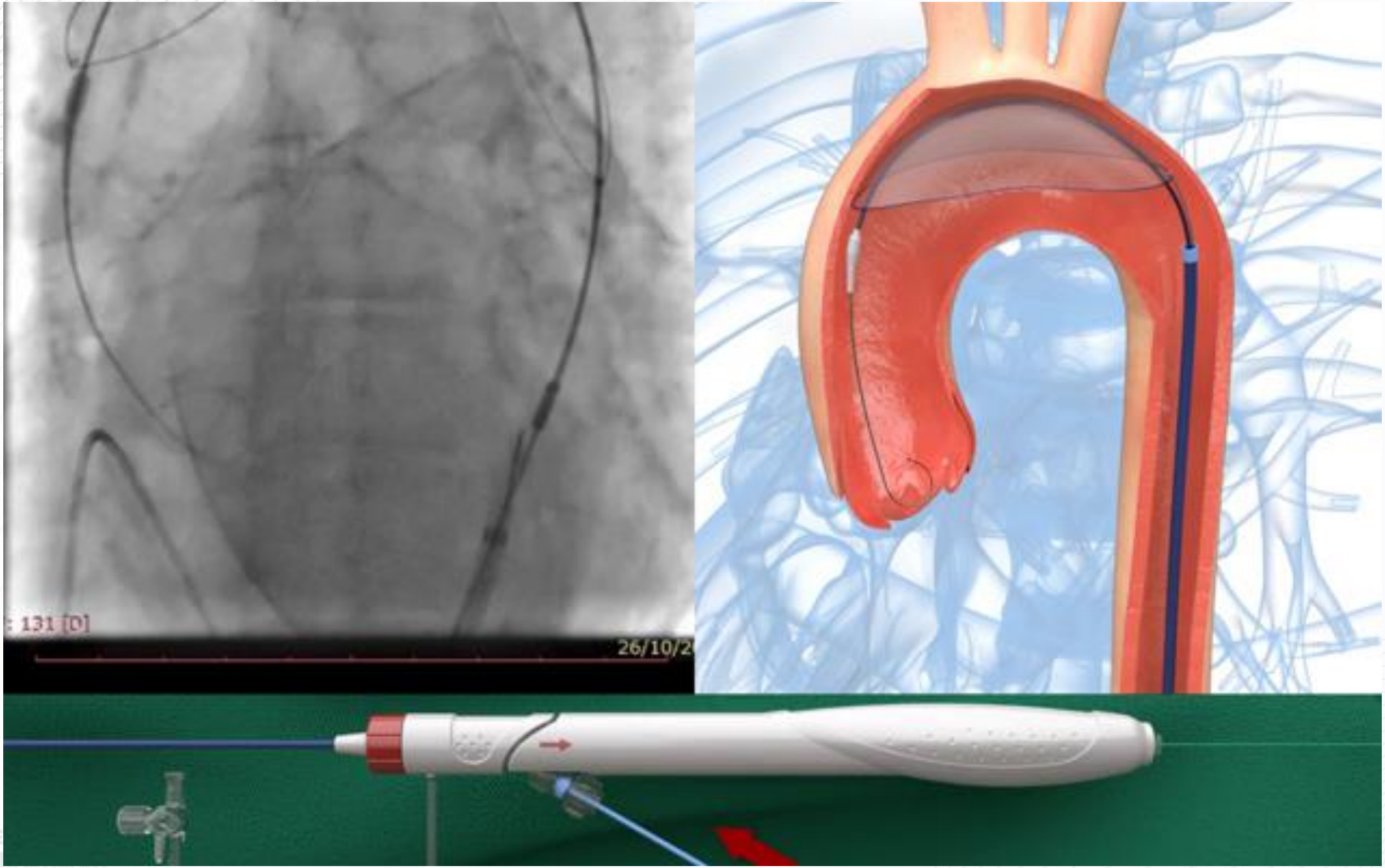
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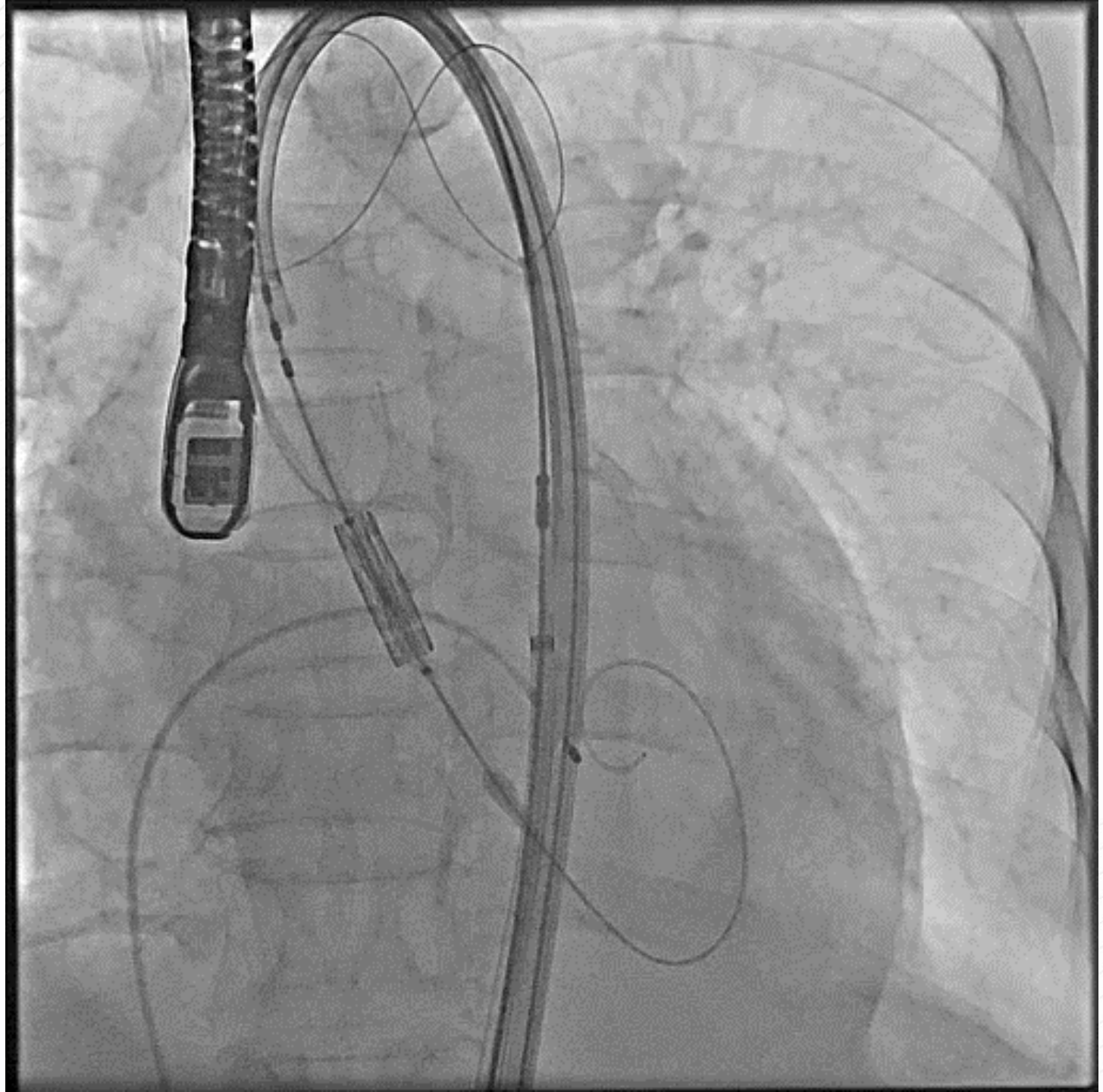

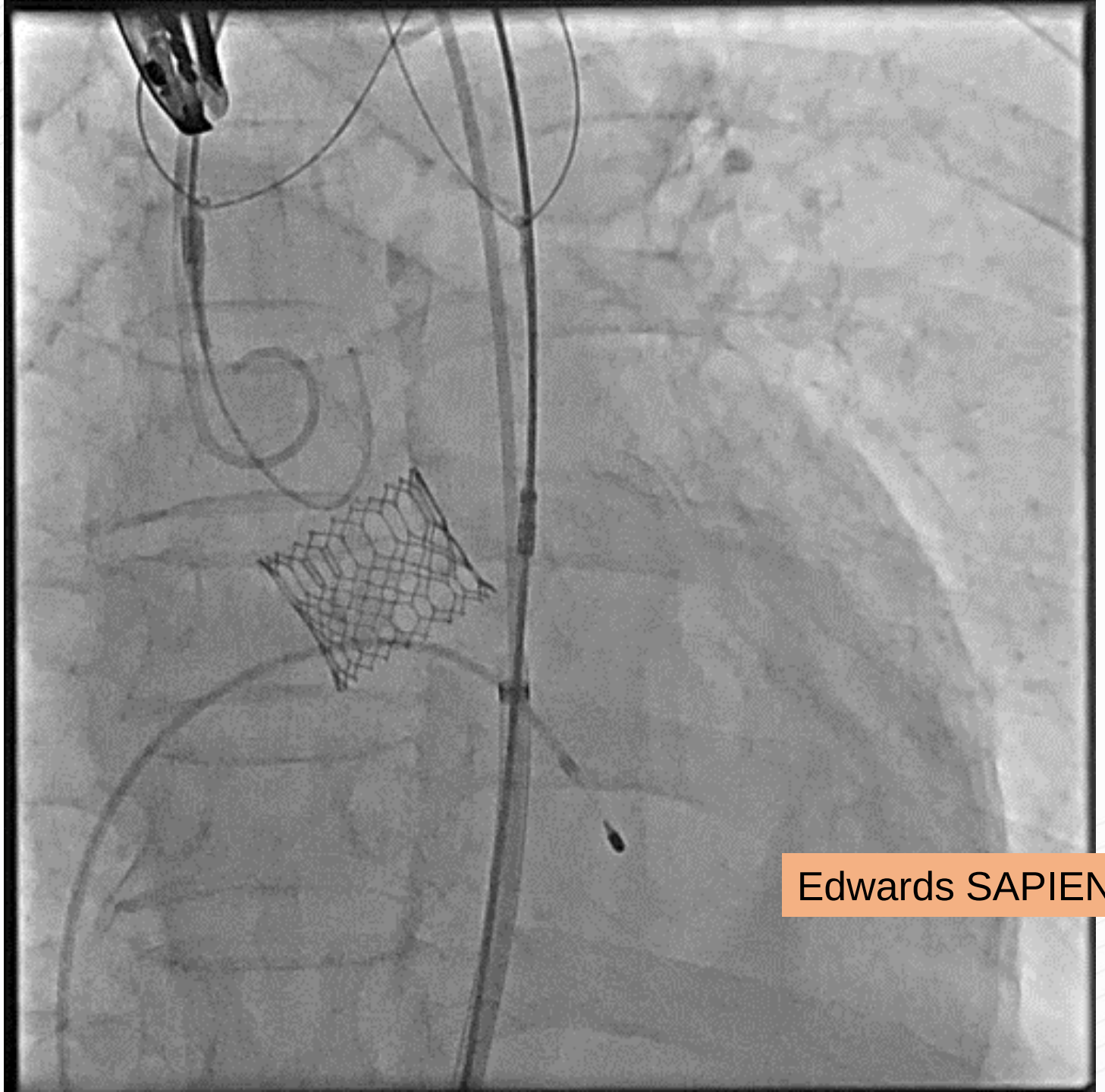

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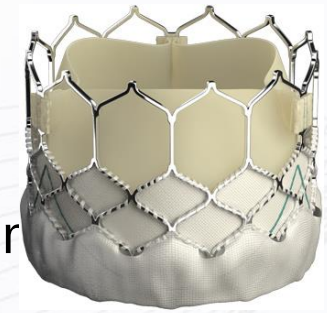

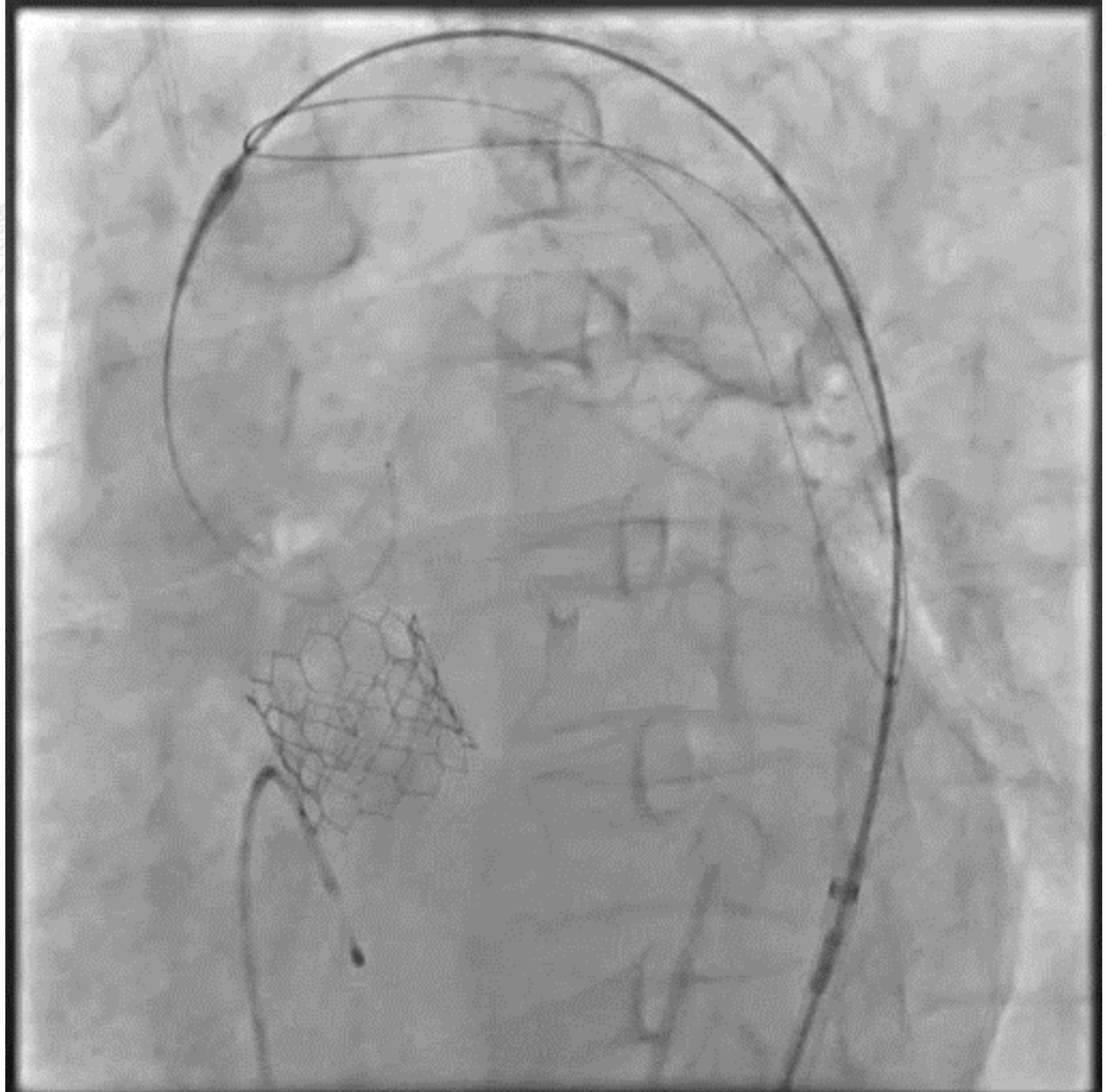

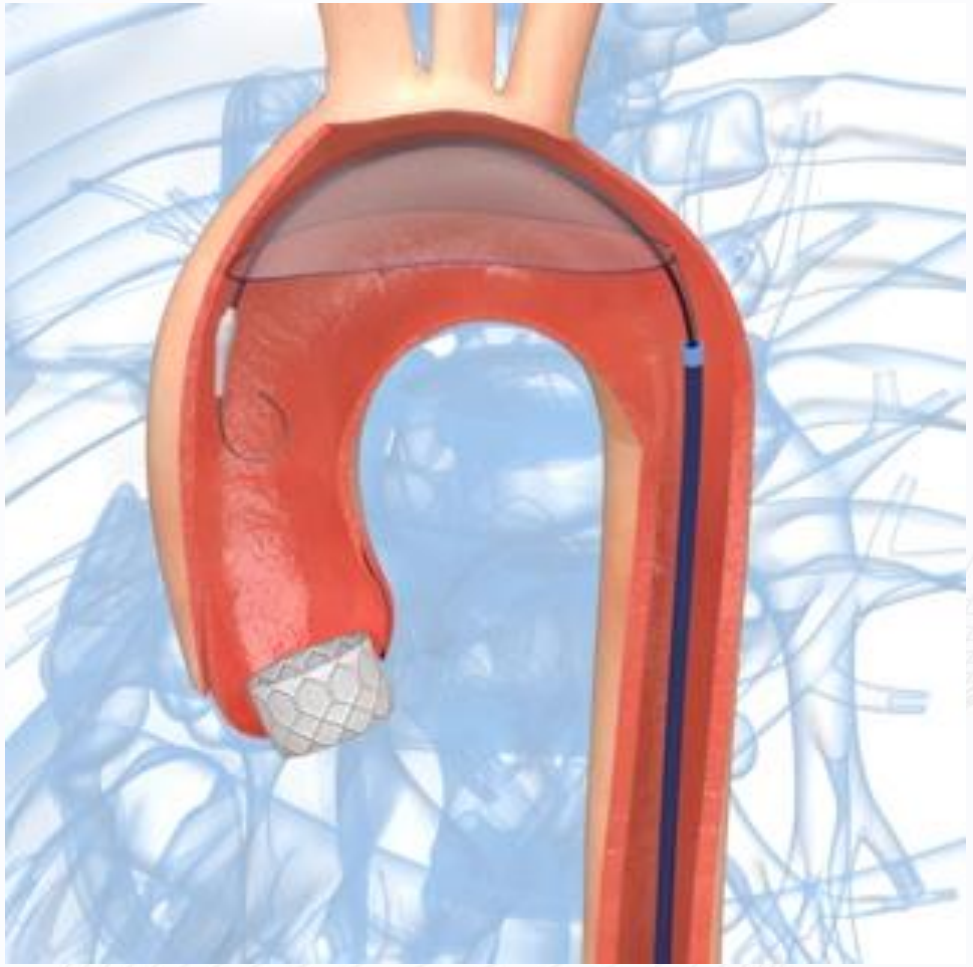

Other considerations

- Preserve right radial access prior to planned TAVI procedures
  - Pre TAVI PCI via L radial
  - Remind anesthetists avoid setting right arterial line
- Secure right arm position during TAVI under LA/MAC
- Potential limitations of Existing Device
  - explained to patient during consent
- PROTECTED TAVR, BHF PROTECT-TAVI and Combined Analysis
- Minimizing thromboembolic risk in the first place#