TCT Connect 2020: Late-Breaking Trials in Structural Heart Valve Interventions

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest, arrangement, or affiliation with the organization(s) listed below:

Affiliation/Financial Relationship	Company
Consulting Fees/Honoraria	Edwards LifeSciences
Consulting Fees/Honoraria	Medtronic
Consulting Fees/Honoraria	Boston Scientific
Consulting Fees/Honoraria	Biotrace Medical
Consulting Fees/Honoraria	Baylis Medical
Consulting and Equity	Keystone Heart, Venus Medtech

TCT Connect 2020

- **Important TAVR Studies**
  - SCOPE II: Acurate neo vs CoreValve Evolut
  - SCOPE I: 1 year results
  - SOLVE TAVI: 1 year results
  - PARTNER 2 V-in-V Registry: 5 year results

- **TAVR Accessory Devices**
  - REFLECT II: TAVR with TriGuard 3 CEPD
  - TVT Registry: Sentinel CEPD

- **TMVR Studies**
  - Global Expand Study: MitraClip NTR and XTR
  - MITHRAS Trial: Iatrogenic ASD closure

SCOPE II Trial Design

23 European Sites

Patients with symptomatic severe aortic stenosis undergoing TAVR as established by the Heart Team
N=796

Randomise 1:1

ACURATE neo
N=398

CoreValve Evolut
N=398

Primary endpoint (noninferiority)
All-cause death or stroke at 1 year

Key secondary endpoint (superiority)
New permanent pacemaker implantation at 30 days

SCOPE II

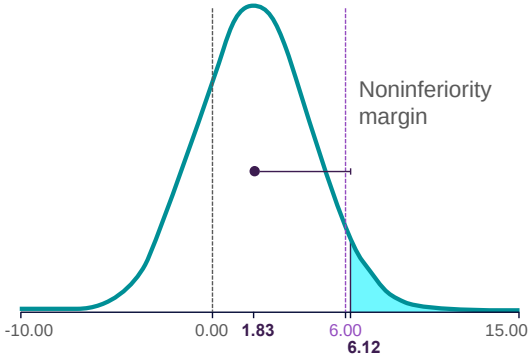
TCT CONNECT

Scope II: Primary Endpoint Missed

Primary endpoint

Death or stroke at 1 year (intention-to-treat)

ACURATE neo: 15.8% | CoreValve Evolut: 13.9%

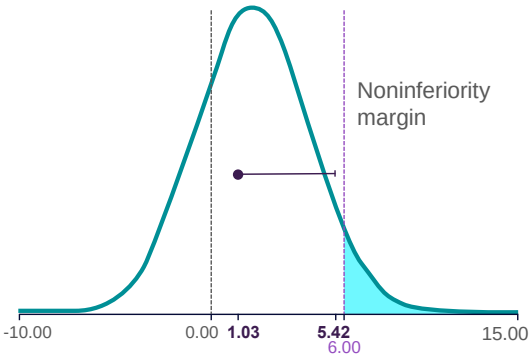


Favours ACURATE ⟷ Favours CoreValve

Absolute risk difference for primary endpoint (%)

Death or stroke at 1 year (per-protocol)

ACURATE neo: 15.3% | CoreValve Evolut: 14.3%



Favours ACURATE ⟷ Favours CoreValve

Absolute risk difference for primary endpoint (%)

Because the results of the intention-to-treat and per-protocol analyses were inconsistent, noninferiority of the ACURATE neo was not established for the primary endpoint

SCOPE II

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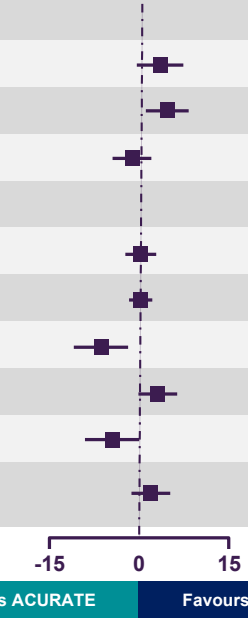
Secondary endpoints at 1 year (intention-to-treat)

Events, n (%)

	ACURATE neo (N=398)	CoreValve (N=398)	Risk difference (95% CI)	p value
Components of primary endpoint				
All-cause death	46 (13%)	33 (9%)	3.5 (-1.0 to 8.0)	0.13
Cardiac death	31 (8%)	14 (4%)	4.5 (1.0 to 8.0)	**0.01**
Stroke	18 (5%)	24 (6%)	-1.6 (-4.8 to 1.6)	0.33
Other secondary endpoints				
Life threatening or major bleeding	12 (3%)	12 (3%)	0.0 (-2.5 to 2.5)	1.00
Myocardial infarction	5 (1%)	4 (1%)	0.3 (-1.3 to 1.8)	0.76
New pacemaker implantation	43 (11%)	71 (18%)	-7.2 (-12.2 to -2.3)	**0.0043**
Hospitalisation for cardiac reasons	26 (7%)	15 (4%)	3.0 (-0.3 to 6.3)	0.079
New left bundle branch block	53 (14%)	73 (19%)	-5.2 (-10.3 to -0.0)	**0.048**
Any tachyarrhythmia resulting in haemodynamic instability or requiring therapy	24 (6%)	17 (4%)	1.9 (-1.3 to 5.2)	0.24



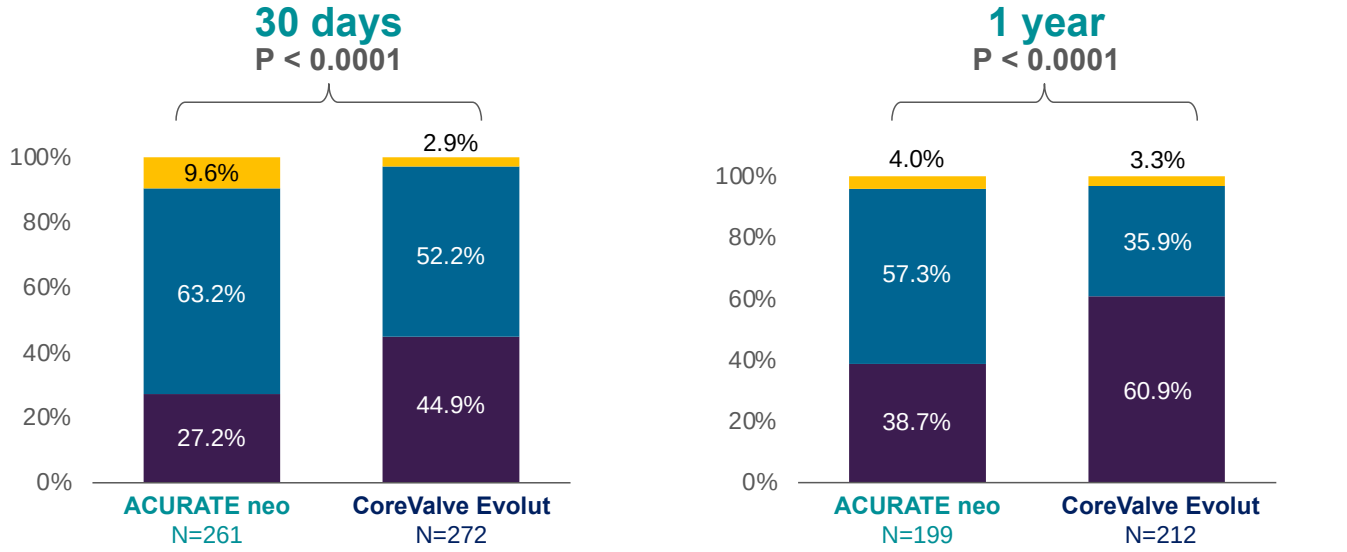
Percentages are Kaplan-Meier estimates or cumulative incidence estimates taking mortality as a competing risk into account

SCOPE II

TCT CONNECT

Aortic regurgitation

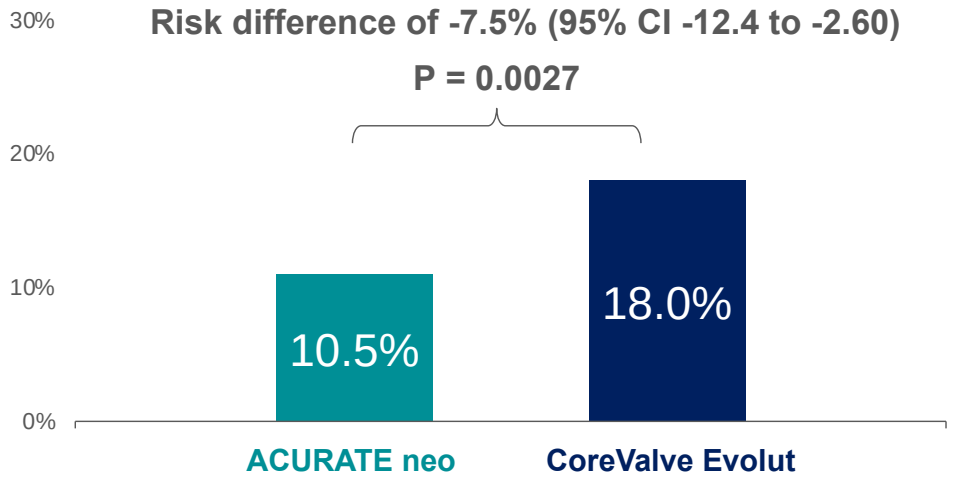
Core lab assessment



SCOPE II

TCT CONNECT

New pacemaker implantation at 30 days (intention-to-treat)



SCOPE II

TCT CONNECT

Acurate Neo new PPM ~10% across multiple studies!

SCOPE I Trial

739 patients with severe, symptomatic aortic stenosis selected for TF TAVR by the Heart Team

Randomization

372 allocated to **ACURATE neo**

367 allocated to **SAPIEN 3**

369 TF TAVR initiated
363 received ACURATE neo
11 multiple valve implantation
2 conversion to SAVR
6 received SAPIEN 3

3 TF TAVR not initiated
(2 deaths, 1 infection)

363 TF TAVR initiated
362 received SAPIEN 3
2 multiple valve implantation
1 received ACURATE neo

4 TF TAVR not initiated
(2 deaths, 1 withdrawal, 1 planned TA TAVR)

11 withdrawal of consent
1 lost-to-follow-up

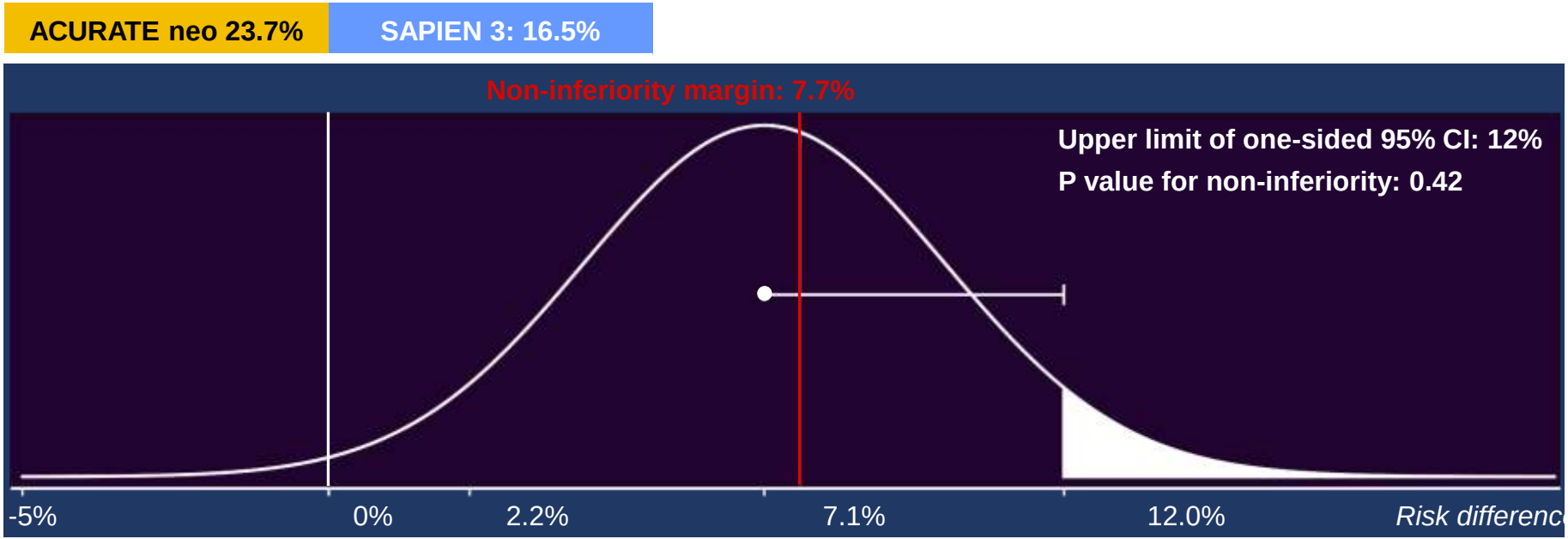
1-year Follow-up

11 withdrawal of consent
1 lost-to-follow-up

358 (96%) Clinical follow-up complete
2 (1%) Clinical follow-up incomplete, but alive

355 (97%) Clinical follow-up complete

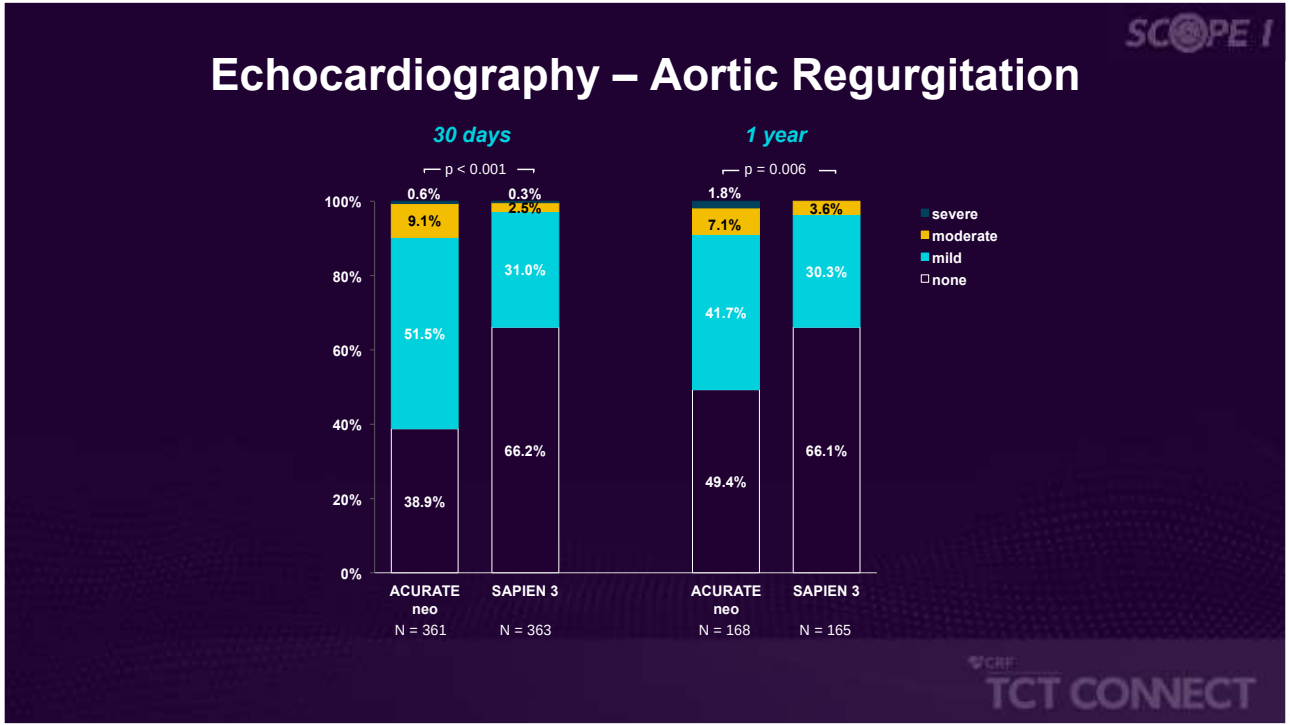
TCT 2019: Primary Endpoint at 30 days



VARC 2 early safety and clinical efficacy

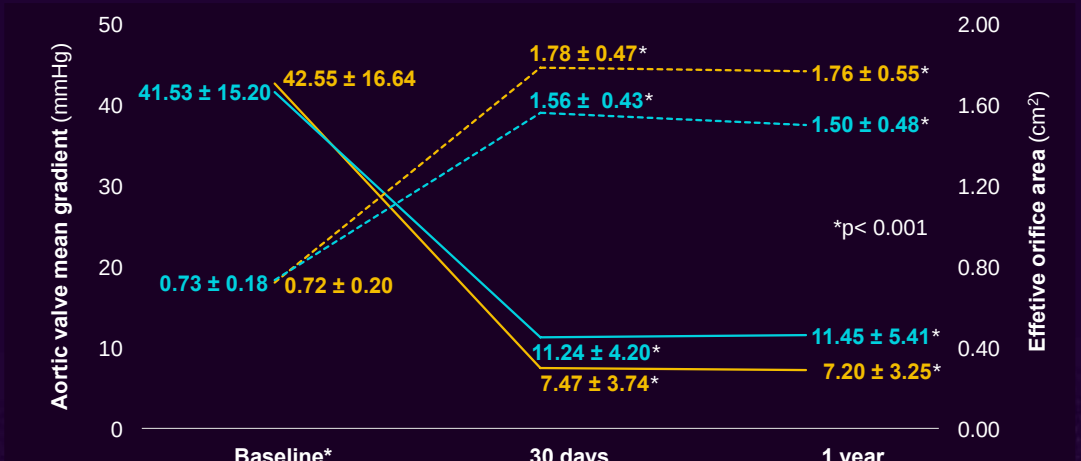
Lanz et al. *Lancet.* 2019;394:1619-1628.

Echocardiography – Aortic Regurgitation



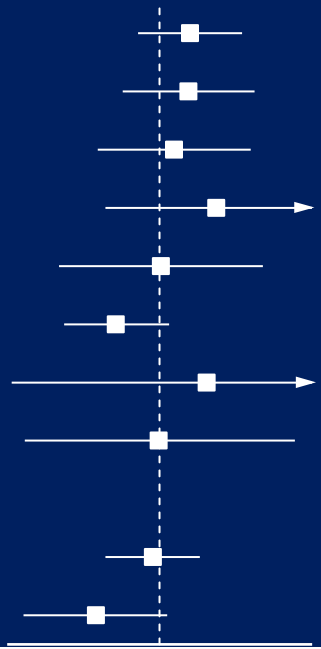
***Incomplete echocardiographic follow-up 1 year**

Echocardiography – mean Gradient & EOA



SCOPE I: Clinical Outcomes at 1 year

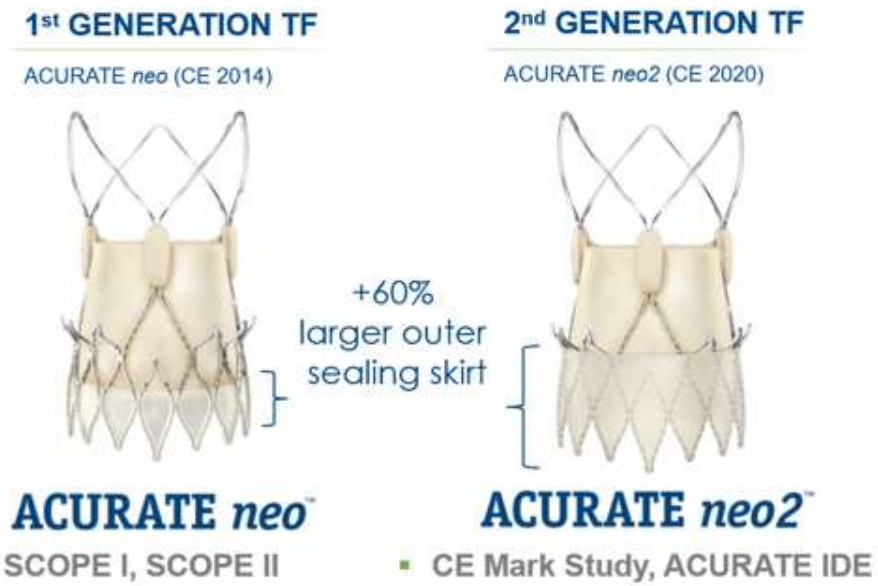
	ACURATE neo	SAPIEN 3	Hazard ratio (95%-CI)	P value
	No. of events/total no. (%)			
All-cause death	40/360 (11.1%)	30/355 (8.5%)		0.25
Cardiovascular death	25/360 (6.9%)	19/355 (5.4%)		0.39
Stroke	17/358 (4.7%)	15/356 (4.2%)		0.71
Disabling stroke	10/358 (2.8%)	6/356 (1.7%)		0.32
Non-disabling stroke	9/358 (2.5%)	30/356 (2.5%)		0.98
Hospitalization for valve-related dysfunction or CHF	28/359 (7.8%)	41/355 (11.5%)		0.10
Valve-related dysfunction requiring repeat procedure	3/358 (0.8%)	2/355 (0.6%)		0.64
Endocarditis	5/360 (1.4%)	5/355 (1.4%)		0.99
Valve thrombosis	0/358 (0.0%)	3/355 (0.8%)		NA
Permanent pacemaker implantation	41/361 (11.4%)	43/357 (12.0%)		0.76
New onset atrial fibrillation/flutter	14/358 (3.9%)	25/355 (7.0%)		0.08



***Not powered for 1 year outcomes!**

Evolution of the Acurate neo to Acurate neo2

- **Learning curve** associated to a newer valve
- **Design changes** implemented since SCOPE I & SCOPE II
  - +60% enlarged sealing skirt
  - Radiopaque Positioning Marker
    - Clear visual reference for easy and accurate positioning
  - Low Profile 14F iSLEEVE™ Expandable Introducer sheath
    - To access small and complex anatomies
- **Optimize Patient and Valve selection**
  - Patient selection is reviewed by the CRC
  - Proper sizing of the valve based on anatomy and calcification (CRC recommendations)



Courtesy Boston Scientific

SOLVE-TAVI – 2 x 2 Factorial Design

Symptomatic Aortic Stenosis with TAVR Indication

CoreValve Evolut R — **Valve Strategy** — **Edwards Sapien 3**

Local Anesthesia — **Anesthesia Strategy** — **General Anesthesia**

1-year Outcomes – Valve Strategy

SOLVE-TAVR

	Evolut R	Sapien 3	p-value Gray's test	Cause specific HR (95% CI)
	n (%)	n (%)		
Composite endpoint*	87 (41.9)	85 (40.4)	0.76	0.95 (0.71-1.28)
All-cause mortality	34 (17.6)	33 (17.0)	0.88	0.96 (0.60-1.55)
Cardiovascular mortality	1 (0.5)	4 (1.8)	0.19	3.89 (0.44-34.67)
Stroke	2 (1.0)	14 (6.9)	0.002	7.13 (1.62-31.32)
Moderate/severe PVL	14 (7.0)	9 (4.5)	0.35	0.63 (0.27-1.45)
Permanent pacemaker implantation	54 (24.7)	44 (20.2)	0.25	0.79 (0.53-1.16)
Time-related safety (VARC-2)	45 (15.6)	64 (20.8)	0.10	1.36 (0.93-1.99)

*Composite of all-cause mortality, stroke, moderate/severe PVL, and permanent pacemaker implantation

1-year Outcomes – Anesthesia Strategy

SOLVE-TAVI

Outcome	Local anesthesia	General anaesthesia	p-value Gray's test	Cause specific HR (95% CI)
	n (%)	n (%)		
All-cause mortality	29 (15.2)	38 (19.4)	0.27	1.31 (0.81 to 2.13)
Cardiovascular mortality	2 (0.9)	3 (1.4)	0.68	1.46 (0.24 to 8.73)
Stroke	6 (3.0)	10 (4.9)	0.33	1.64 (0.60 to 4.49)
Myocardial Infarction	2 (1.0)	1 (0.5)	0.56	0.50 (0.05 to 5.45)
Infection requiring antibiotics (at 6 months)	52 (17.7)	56 (18.8)	0.72	1.07 (0.73 to 1.55)
Acute kidney injury	28 (12.2)	27 (11.7)	0.87	0.96 (0.57 to 1.63)
Time-related safety (VARC-2)	54 (17.6)	55 (18.8)	0.72	1.07 (0.73 to 1.55)

PARTNER 2 Valve-in-Valve Registries: 5 year data

Valve and Procedural Characteristics

Surgical Bioprosthesis Age	% (n/N)
< 5 years	6.8 (25/365)
5-10 years	27.1 (99/365)
> 10 years	66.0 (241/365)

Mode of Degeneration	
Stenosis	55.0 (197/358)
Regurgitation	23.7 (85/358)
Mixed	21.2 (76/358)

Surgical Valve Type	
Bioprosthetic Stented	93.1 (336/365)
Homograft	6.0 (22/365)
Other	0.8 (3/365)

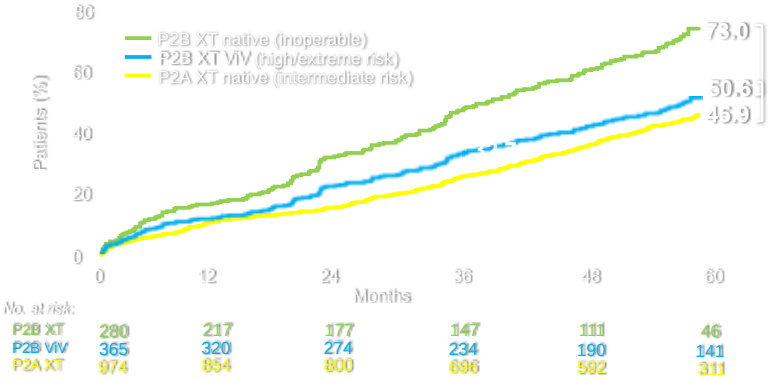
Labeled Surgical Valve Size	% (n/N)
21 mm	26.7 (95/356)
23-25 mm	60.8 (216/356)
>25 mm	12.6 (45/356)

SAPIEN XT Size	
23 mm	69.0 (252/365)
26 mm	31.0 (113/365)

Access	

Results

All-Cause Death ViV vs. Other Studies

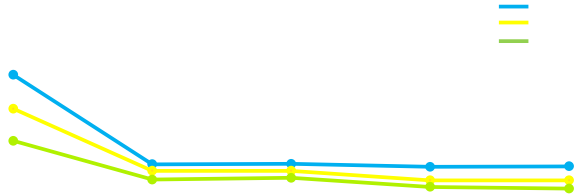


Valve-in-valve TAVR compares favorably with native TAVR with SAPIEN XT

5 year Echocardiographic Analysis: Hemodynamics Stable over times

Results

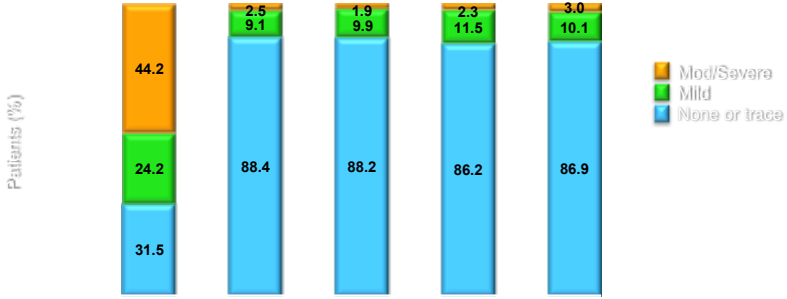
Mean Gradient by Failure Mode



Stenosis	191	185	141	99	56
Mixed	75	69	55	32	18
Regurgitation	83	78	71	40	20

Results

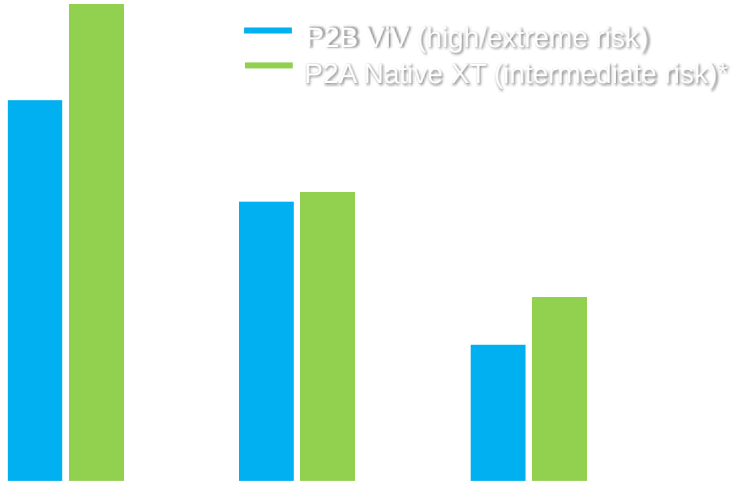
Total Aortic Regurgitation



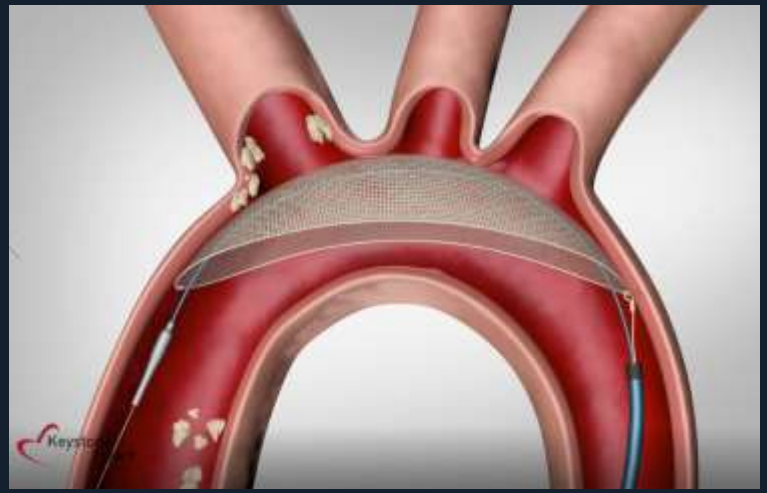
No. of echos:

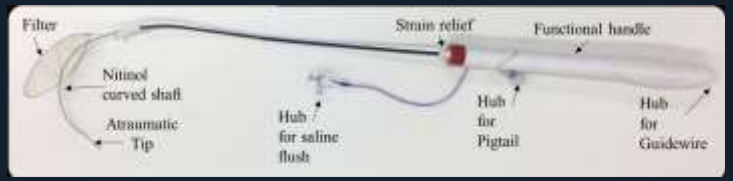
Results

HVD and BVF at 5 Years: ViV vs. Native XT



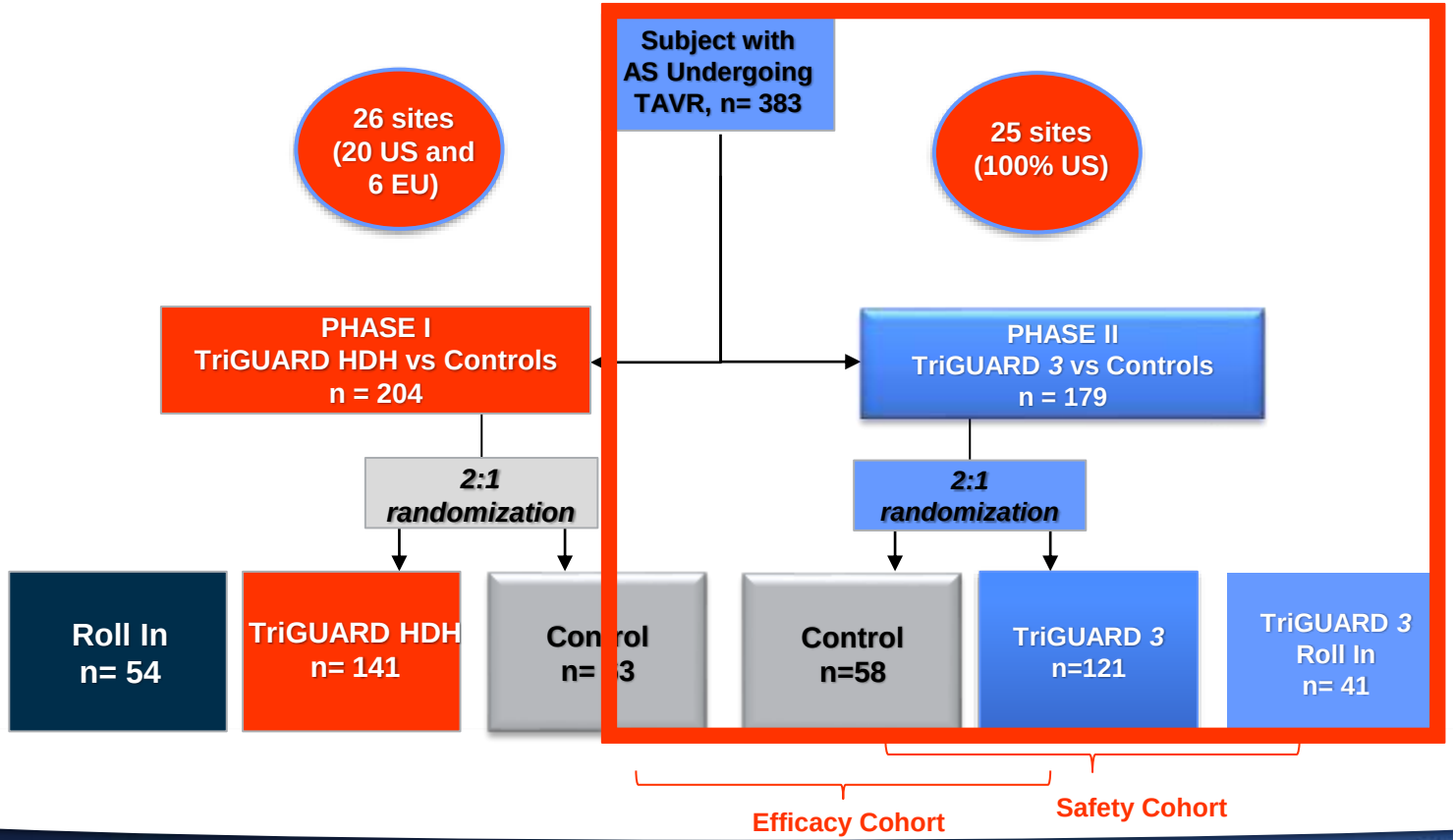
Cerebral Embolic Protection: TriGUARD *3*



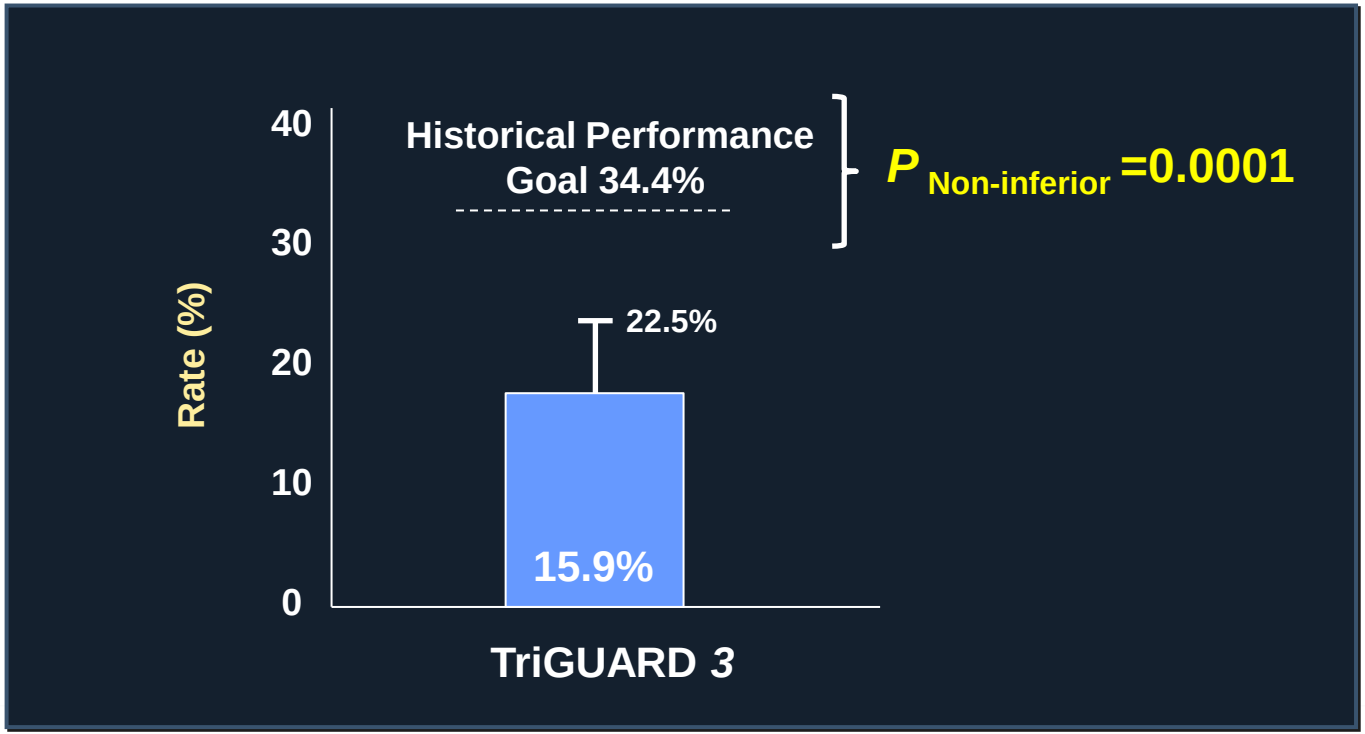


- Self-positioning, nitinol frame without stabilizers
- PEEK mesh (pore size 115 x 145 µm)
- Filter area = 68.3 cm^2
- 8 Fr OTW delivery
- Accommodates a diagnostic pigtail

REFLECT II Trial: TriGUARD 3



Primary Safety: VARC-2 Safety Composite at 30d

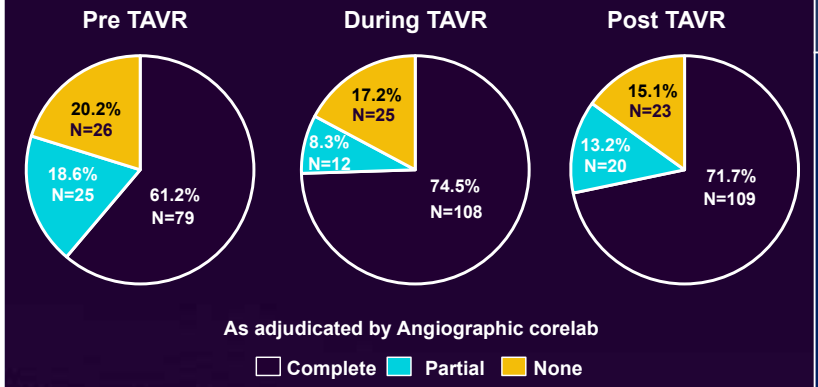


Primary Efficacy : Hierarchical composite (Finkelstein Schoenfeld methodology)

	TriGUARD *3*	Pooled Controls	*P* value
Primary Outcomes	112	119	
Primary Efficacy Score	-8.58 ± 120.76	8.08 ± 116.51	0.857
Win percentage, %	45.7	54.3	–
Component event rates			
All-cause mortality or any stroke at 30 days, %	9.8	6.7	0.475
NIHSS worsening predischarge, %	14.1	7.6	0.176
Cerebral ischemic lesions, %	85.0	84.9	1.000
Total cerebral lesion volume, mm^3, Median (IQR)	215.39 (68.13, 619.71)	188.09 (52.08, 453.12)	0.405

Prespecified primary efficacy population was randomized TG3 vs pooled controls
Win percentage= wins/wins+losses (removes ties)

TriGUARD *3* Performance and Cerebral Coverage



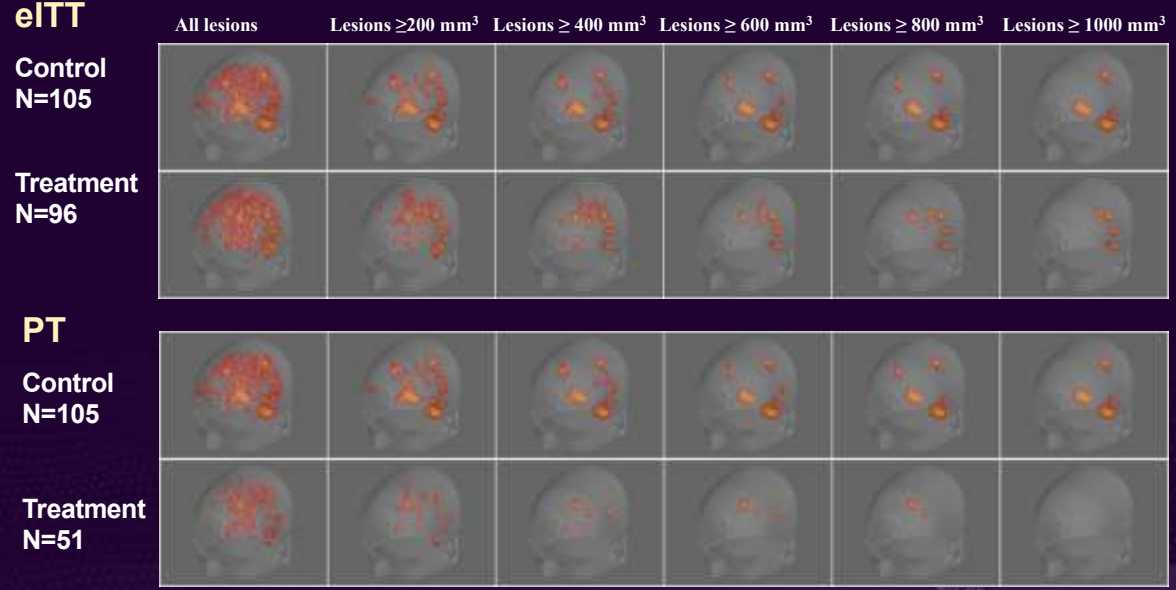
Performance Measures	Combined TriGUARD *3* (N=157)
Successful deployment	100%
Successful on 1st attempt	98.1%
Technical Success	71%
Procedure Success	69.7%
Device Interaction	9.6%
Deployment Time Mean ± SD	2.81 ± 5.69

Full Coverage Throughout: 59.3%
All devices successfully deployed and retrieved

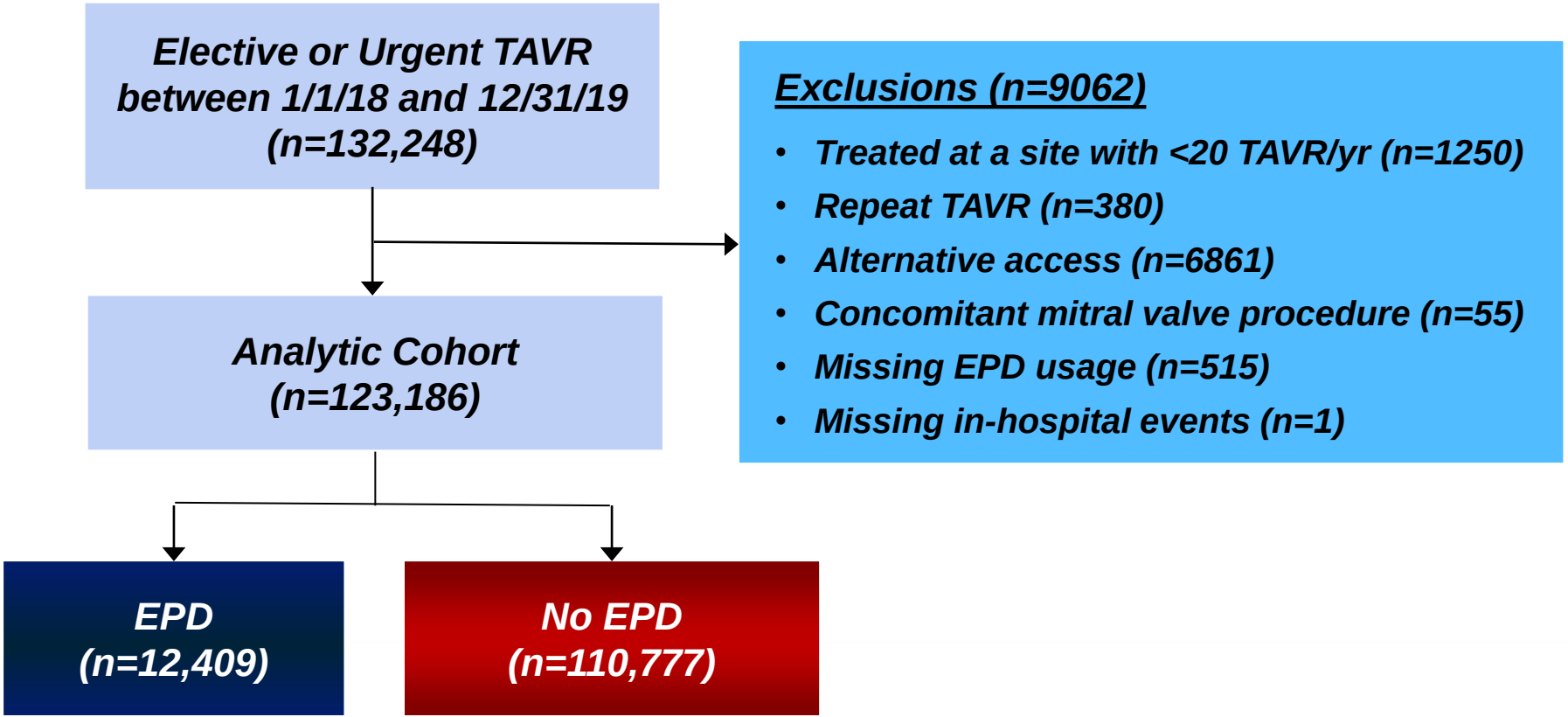
Technical Success: Full coverage in the absence of device interaction
Procedure success: Technical success without TG3-related in-hospital MACCE

Post-hoc Analysis

Suprathreshold Lesion Volume Analysis in eITT and PT

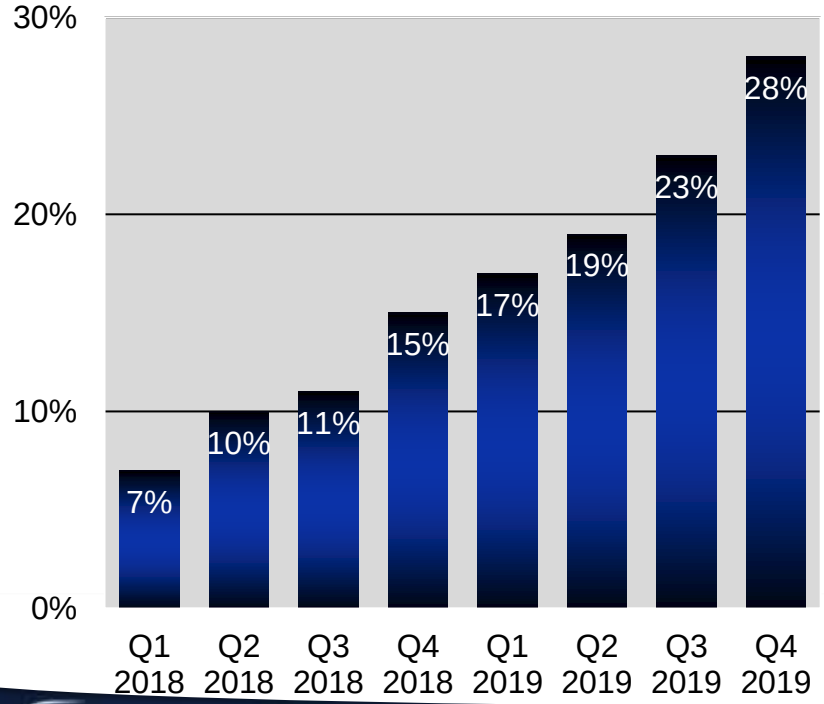


TVT Registry Analysis of CEPD with Sentinel

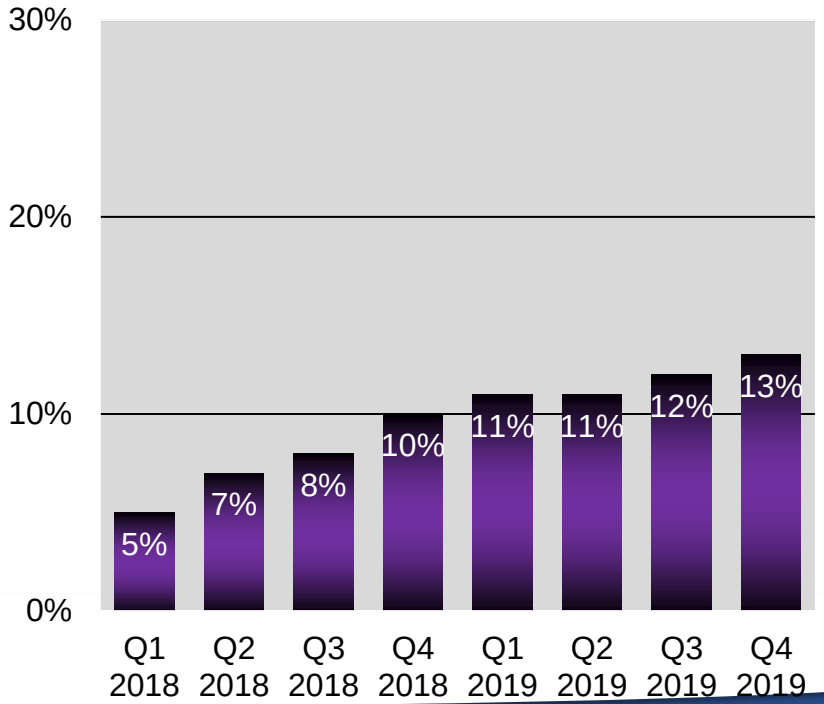


CEPD Utilization by Calendar Quarter

Proportion of Hospitals Using EPD

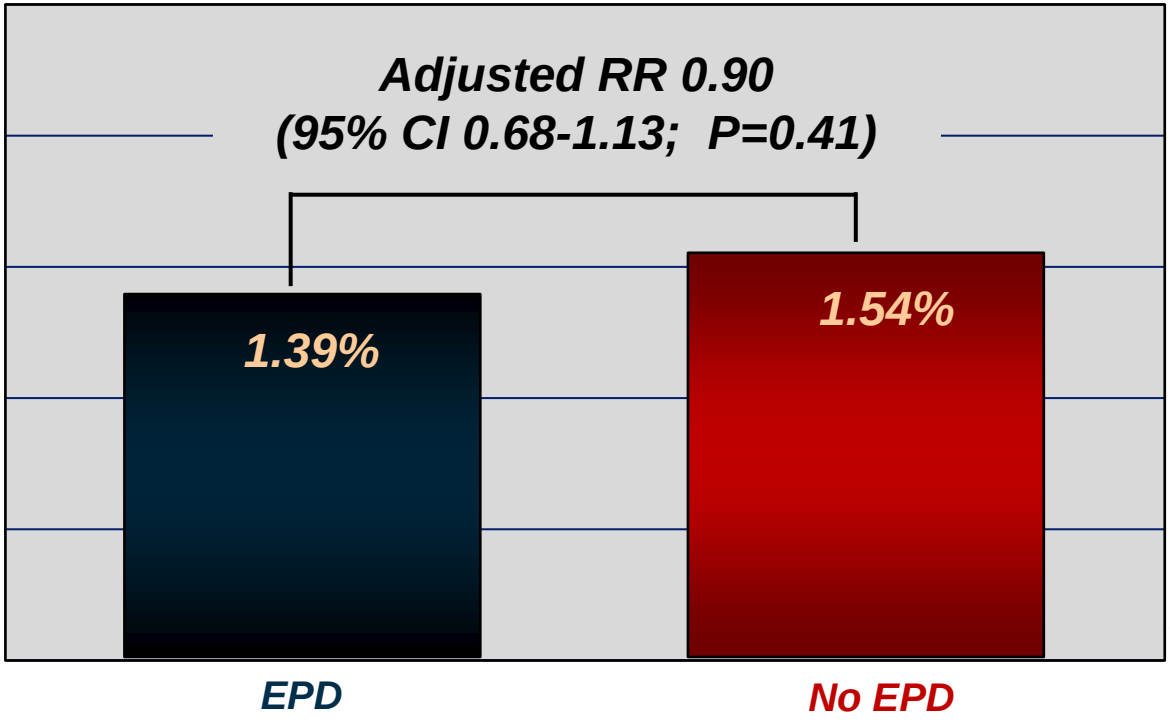


Proportion of Patients Receiving EPD

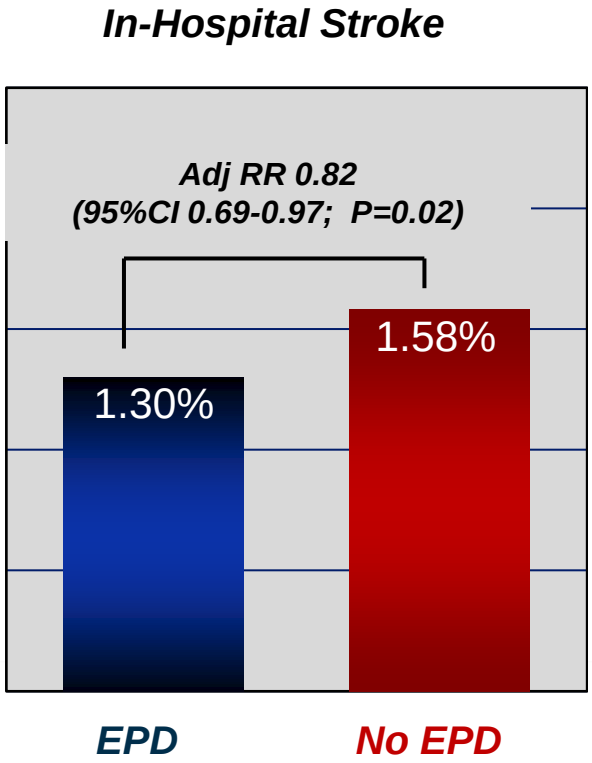


Results: Instrumental Variable Analysis

Primary Endpoint: In-Hospital Stroke



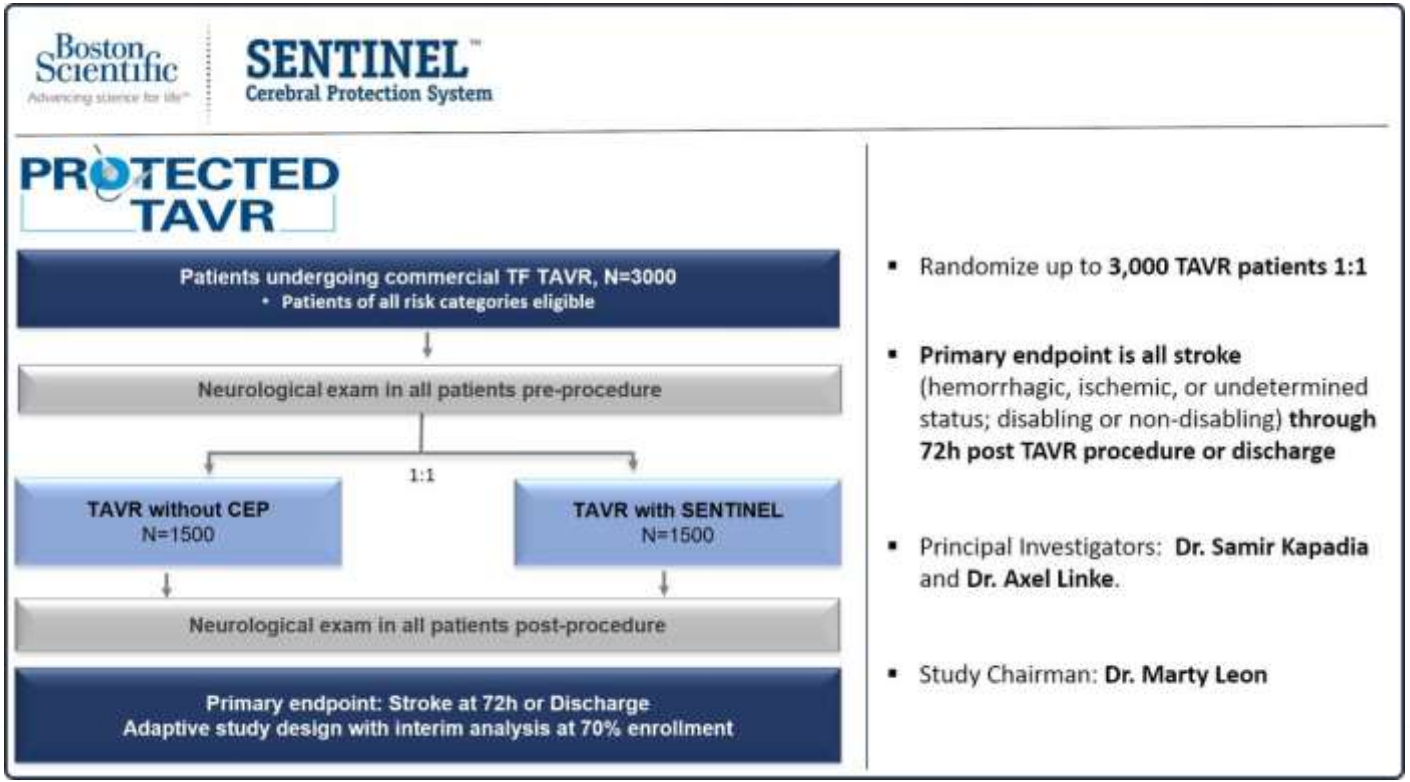
Results: Propensity-Weighted Analysis



	EPD	No EPD	Adjusted RR (95% CI)	Adj P-Value
In-Hosp. Outcomes				
Death or Stroke	2.1%	2.5%	0.84 (0.73-0.98)	0.03
Death	0.9%	1.1%	0.86 (0.66-1.10)	0.23
Device Success	97.3%	97.3%	1.01 (0.76-1.35)	0.93
Major Bleeding	4.7%	4.3%	1.09 (0.95-1.24)	0.22
GI or GU Bleed	0.6%	0.5%	1.29 (0.92-1.81)	0.14
30-day Outcomes				
Stroke	1.9%	2.2%	0.85 (0.73-0.99)	0.04
Death	1.7%	2.2%	0.78 (0.64-0.95)	0.01

*All results risk-adjusted based on overlap propensity weights

Large scale, randomized stroke trial



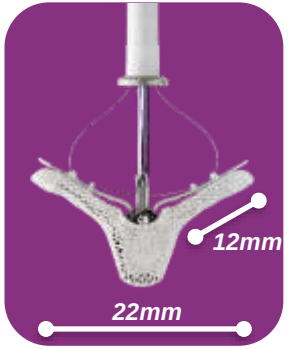
Global Expand Study: Core-Lab/CEC adjudicated outcomes

- MitraClip™ NTR and XTR Systems were introduced in 2018 with the goal to improve the overall ease of use with the modified delivery catheter, and to assist in leaflet grasping with the longer clip arms of the XTR clip.

- EXPAND Study was initiated to evaluate contemporary real-world clinical outcomes in subjects treated with the MitraClip™ NTR and XTR Systems.

MitraClip NTR

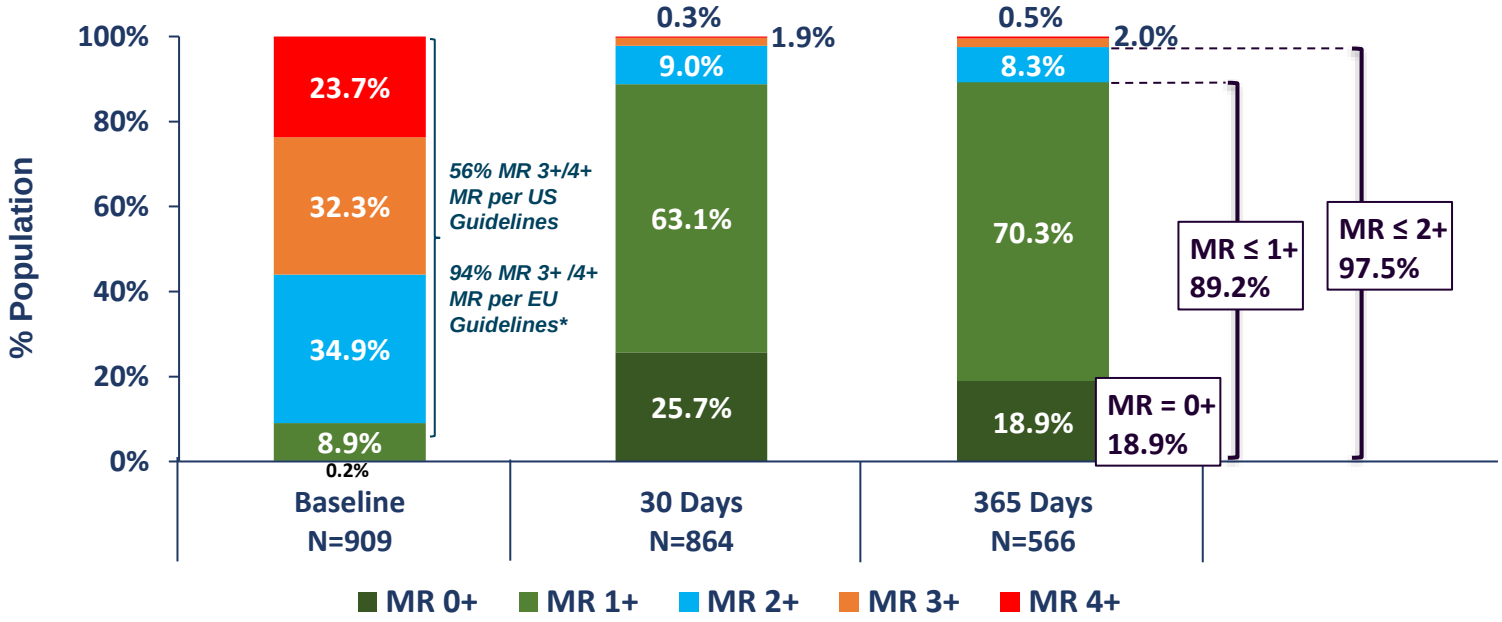
Identical to Original MitraClip NT and Classic size with improved delivery system



MitraClip XTR

Longer arms for easier grasp and better reach, with an improved delivery catheter system

1-year Core Lab Adjudicated MR Severity

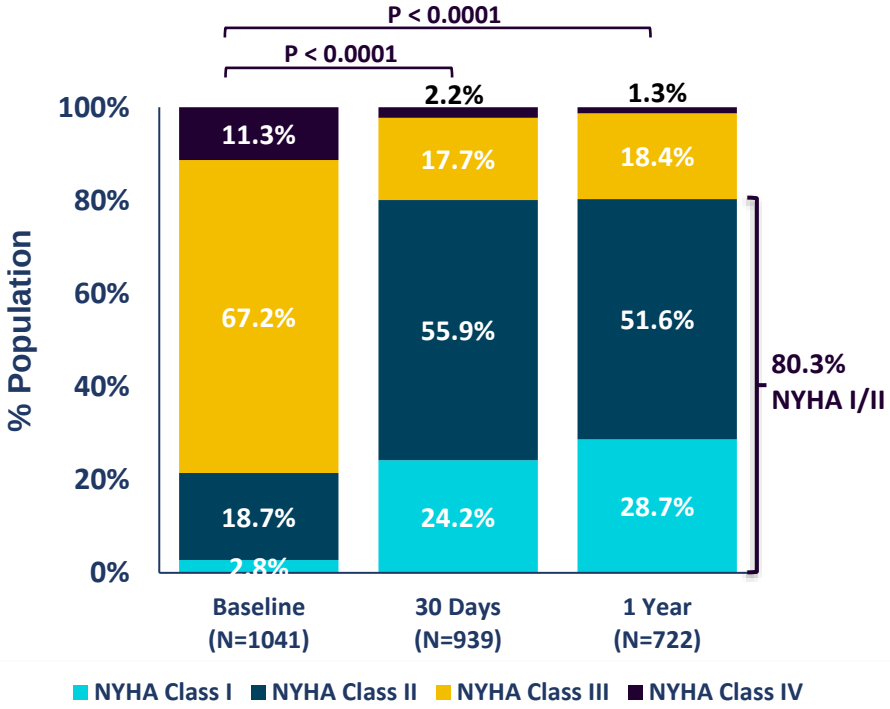


- **Significant MR Reduction from baseline through 1 year was maintained; Trace MR was achieved in 18.9%, MR ≤ 1+ was achieved in 89.2% and MR ≤ 2+ was achieved in 97.3% at 1 year follow up.**

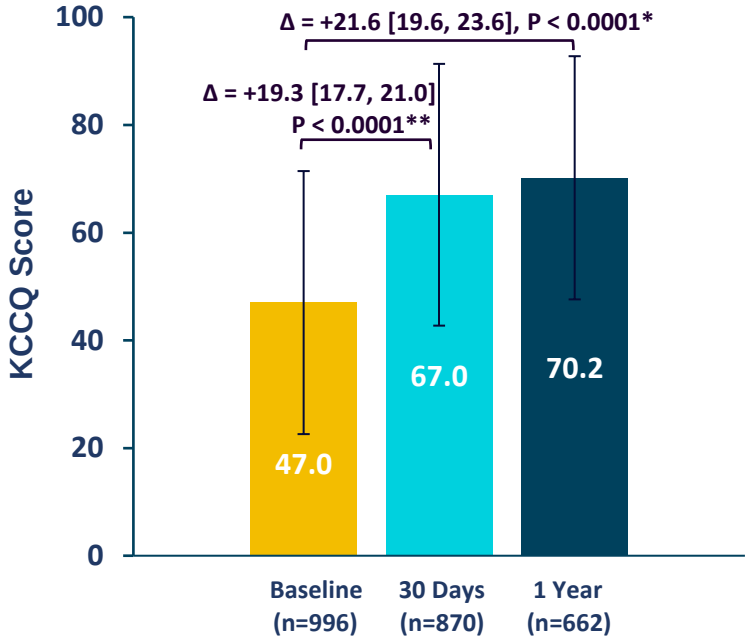
**von Bardeleben et al. ESC 2019*

Functional and Quality of Life Improvement

NYHA Class Change

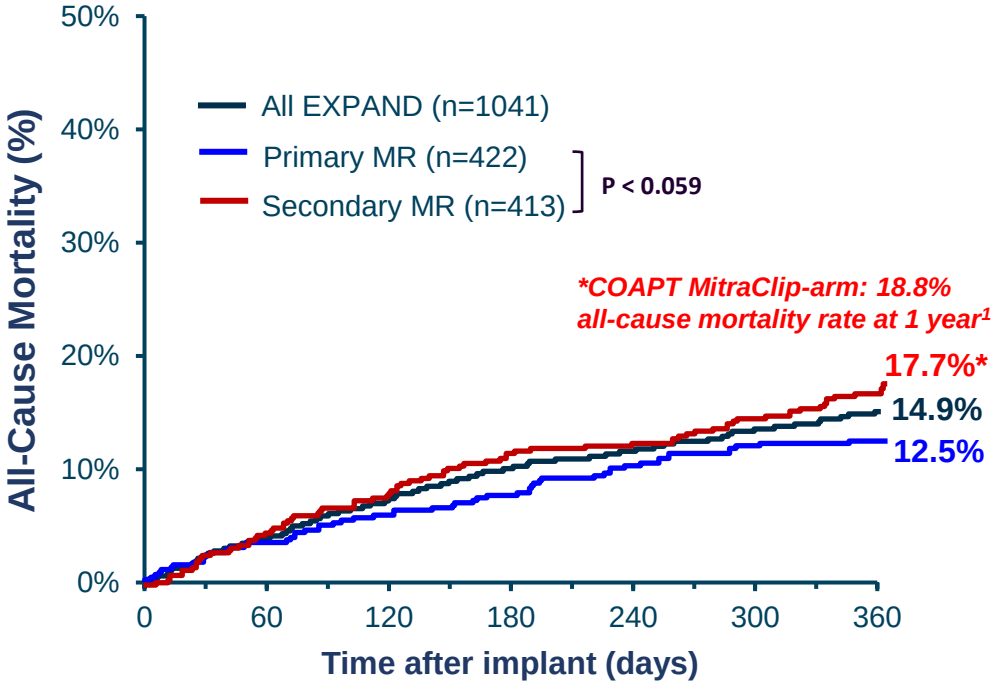


Change in KCCQ Score



**Pairwise comparison between Baseline and 1 Year (n=648); Baseline and 30 day (n=853); 95% CI shown in brackets*

1 Year Mortality and Adverse Events



# at Risk:				
All EXPAND	1041	1002	890	583
Primary MR	422	406	376	256
Secondary MR	413	399	341	212

Adverse Events	All EXPAND n=1041	PMR n=422	SMR n=413
All-cause Mortality	14.9% (147)	12.5% (51)	17.7% (68)
MI	1.2% (12)	0.7% (3)	1.5% (6)
Stroke	1.7% (18)	2.4% (10)	1.2% (5)
SLDA**	1.7% (18)	2.4% (10)	1.9% (8)
Leaflet Injury**	0.4% (4)	0.5% (2)	0.5% (2)
MV Stenosis	0.5% (5)	0.7% (3)	0.5% (2)
MV Reintervention	1.9% (20)	2.1% (9)	1.5% (6)

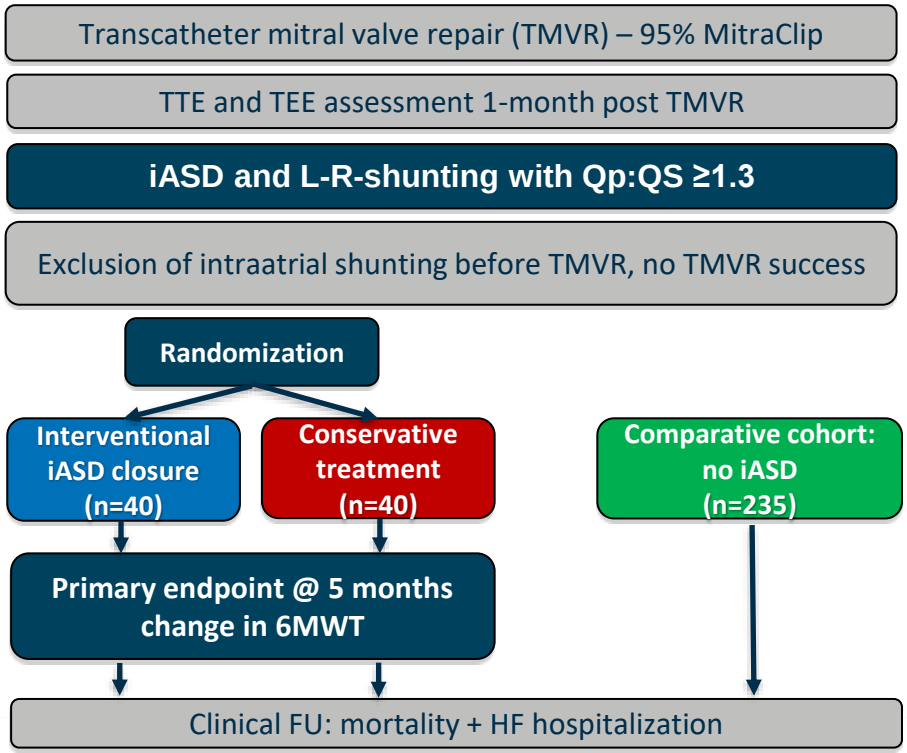
***Single leaflet device attachment (SLDA) and leaflet injury adjudicated by an independent physician committee based on procedural and follow up images, clinical and surgical reports*

[1]*Stone et al. NEJM;379:2307-2318*

MITHRAS Trial Design

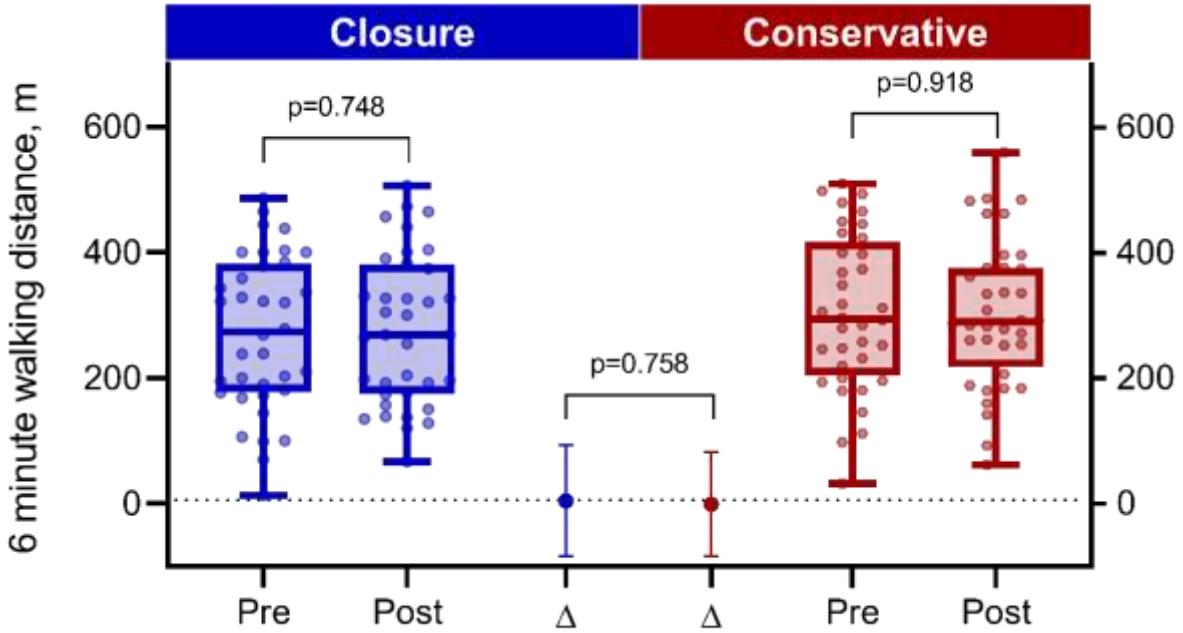
Design

- **Design: Prospective, single-center, investigator initiated, unblinded randomized trial**
- **Population: Patients with persistent iASD and relevant L-R-shunting (Qp:Qs ≥1.3) 1-month post transcatheter mitral valve repair**
- **Primary endpoint: I2T analysis: group difference of change in 6-minute walking distance (6MWT) at 5 months**
- **Powered to detect a 55 m difference in 6MWT between treatment groups with 80% power, α=0.05**

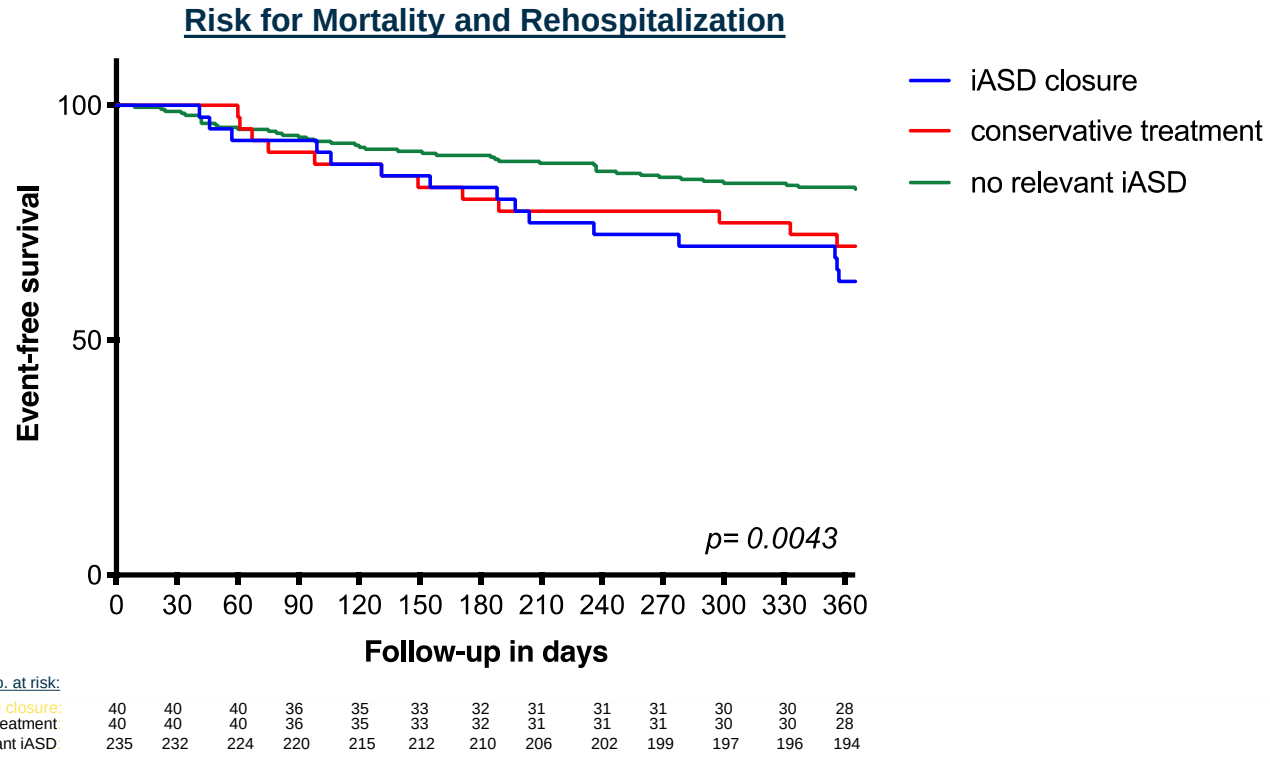


Primary Endpoint

Group difference of change in 6-minute walking distance at 5 months



Randomized vs. Comparative Cohort (no iASD)



Conclusions:

- **TCT Connect 2020 Structural Heart Valve Studies**

- **TAVR studies:**
  - **Scope I and II Trials**
  - **Additional studies reassuring regarding contemporary devices and practices**

- **CEPD: REFLECT II Trial**
  - **TVT registry analysis sets stage for PRETECTED TAVR**

- **Mitral: MitraClip studies**
  - **Global Expand and Mithras reassuring regarding contemporary devices and practices**