PORTICO IDE CLINICAL TRIAL with FlexNav™

Primary Outcomes of the PORTICO Randomized IDE Trial:

Portico Vs. Commercially Available Transcatheter Aortic Valves in High and Extreme Risk Patients

Gregory P. Fontana, MD, FACC, FACS

on behalf of PORTICO IDE Investigators

The CardioVascular Institute
Los Robles Regional Medical Center
Hospital Corporation of America

Disclosure Statement of Financial Interest

I, Gregory P. Fontana have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

- Abbott: National Principal Investigator, Consultant, Structural Heart SAB, Proctor
- Medtronic: Principal Investigator, Consultant, Proctor
- LivaNova: Consultant, Proctor

PORTICO IDE Trial Background

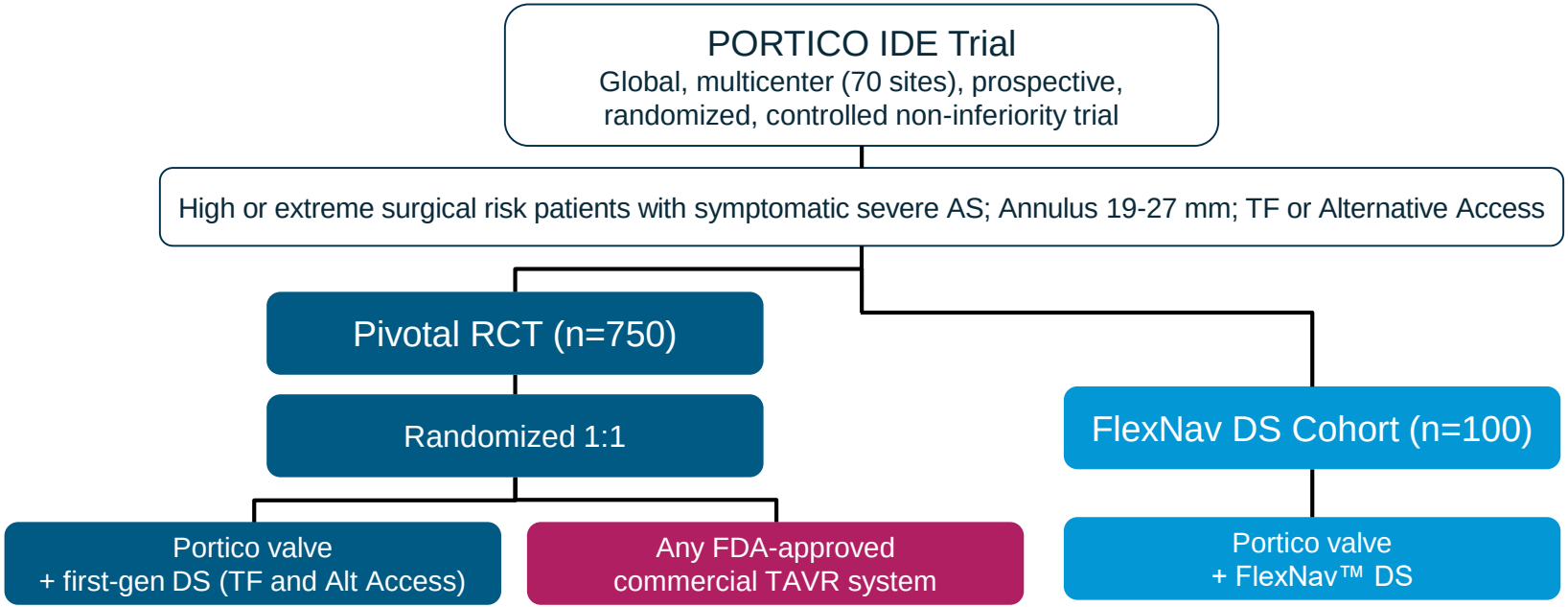
PORTICO IDE CLINICAL TRIAL with FlexNav™

- The PORTICO IDE trial was initiated in 2014 to establish safety and effectiveness of the Portico™ Transcatheter Aortic Valve System in high or extreme surgical risk patients with symptomatic severe AS
- Only 2 transcatheter aortic valves (SAPIEN™ and CoreValve™) were approved for this patient population
- Key differentiating features of the Portico valve*:
  - Intra-annular, self-expanding design
  - Fully recapturable, repositionable and retrievable
  - Large cell geometry
  - Minimal protrusion into LVOT

Patient annulus (mm)	19	21	23	25	27
Valve size (mm)	23	25	27	29	

PORTICO IDE Trial Design

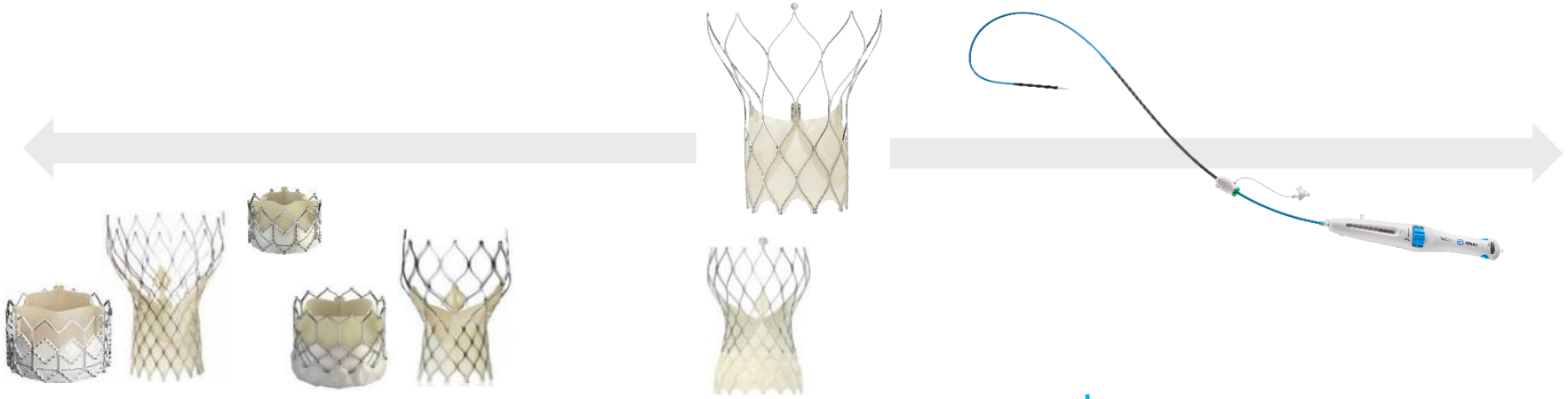
PORTICO IDE CLINICAL TRIAL with FlexNav™



The trial was funded by Abbott (formerly St Jude Medical)

PORTICO IDE Trial Timeline

PORTICO IDE CLINICAL TRIAL with FlexNav™



Pivotal RCT
Enrollment began May 2014

pause

Pivotal RCT
Enrollment complete Oct 2017

FlexNav DS Cohort
Enrollment Nov 2018- Jun 2019

PMA Submission

2014	2015	2016	2017	2018	2019	2020

PORTICO IDE Trial Oversight

PORTICO IDE CLINICAL TRIAL with FlexNav™

Co-Principal Investigators	Raj Makkar, MD (Cedars-Sinai Medical Center) Gregory Fontana, MD (Los Robles Regional Medical Center)
SSC	Raj Makkar, MD (Cedars-Sinai), Gregory Fontana, MD (Los Robles Regional Medical Center), Ravi Ramana, MD (Advocate Christ) Hemal Gada, MD (Pinnacle Health), Stephen Worthley, MD (Genesis Care), Ray Matthews, MD (Keck Medical Center of USC), Michael Reardon, MD (Houston Methodist Hospital), Mark Cunningham, MD (Keck Medical Center of USC), Christian Shultz, MD (Washington Hospital), Mark Russo, MD (Newark Beth Israel)
CT Core Lab	Cedars-Sinai Heart Institute (Hasan Jilaihawi, MD, Tarun Chakravarty, MD, Rahul Sharma, MD)
Echo Core Lab	Medstar Health Research Institute (Director: Neil Weissman, MD)
DSMB	BAIM Institute for Clinical Research (Chair: Deepak Bhatt, MD, MPH)
CEC	Duke Clinical Research Institute (DCRI) (Chair: Rajendra Mehta, MD, MS)

PORTICO IDE Trial Eligibility Criteria

PORTICO IDE CLINICAL TRIAL

with FlexNav™

Inclusion Criteria

- Severe symptomatic aortic stenosis
  - Initial AVA ≤1.0 cm^2 (or indexed EOA ≤0.6 cm^2/m^2) AND mean gradient >40 mmHg or jet velocity >4 m/sec or DVI <0.25
  - NYHA functional class II or greater
- High or extreme risk for SAVR
  - STS ≥8% or deemed by 2 cardiac surgeons to be high or extreme risk due to other medical factors

Exclusion–Clinical

- Prior MI or PCI (<30 days); upper GI bleeding (<3 months); stroke, TIA or active bacterial endocarditis (<6 months)
- Mixed aortic valve disease
- Severe ventricular dysfunction (LVEF <20%)
- Creatine >3.0 mg/dl and/or ESRD
- Life expectancy <1 year

Exclusion–Anatomic

- Significant aortic disease, including abdominal aortic or thoracic aneurysm
- Non-calcified aortic annulus
- Severe obstructive calcification, or severe tortuosity of vessels

Pivotal RCT: Endpoints

PORTICO IDE CLINICAL TRIAL

Primary Safety Endpoint Composite

- All-cause mortality
- Disabling stroke
- Major vascular complications
- Life-threatening bleeding requiring transfusion or
- Acute kidney injury requiring dialysis at 30 days

➢ ***Non-inferiority margin: 8.5%***

Primary Effectiveness Endpoint Composite

- All-cause mortality or
- Disabling stroke at 1 year

➢ ***Non-inferiority margin: 8.0%***

Secondary Endpoints at 1 year

- Severe aortic regurgitation
- KCCQ score
- Moderate or greater aortic regurgitation
- 6-minute walk test

Data from PARTNER I and CoreValve US Pivotal trials were used to establish non-inferiority criteria for safety and effectiveness

Pivotal RCT: Primary Endpoint Analyses

PORTICO IDE CLINICAL TRIAL

- **Primary endpoint analyses performed on an intention-to-treat (ITT) patient population**

Intention-to-Treat:	*All randomized subjects*

Additional analyses performed on:

As Treated:	*All ITT subjects that had treatment initiated, defined as the subject entering the procedure room*
Per Protocol:	*All ITT subjects that were successfully implanted with the assigned valve and did not have major deviations for inclusion or exclusion from the study*

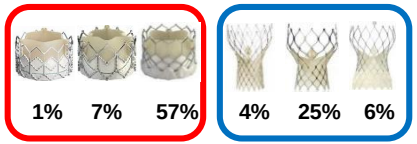
Pivotal RCT: Patient Flow

PORTICO IDE CLINICAL TRIAL

750 randomized subjects enrolled from 52 sites in US and AUS between May 2014 to Oct 2017

750 Randomized (ITT)

Portico valve	Commercial valve
381 Assigned Portico valve	369 Assigned Commercial valve
3 Did not meet eligibility criteria 2 Withdrew informed consent 1 Investigator decision	3 Withdrew informed consent 2 Died before procedure 1 Did not meet eligibility criteria 1 Randomized after subject expired
375 Treatment Initiated	362 Treatment Initiated
2 Died during implant procedure 1 Converted to SAVR 1 Unable to gain vascular access	1 Converted to SAVR
371 Implanted	361 Implanted
30 Day FU: 97.5% 1 Year FU: 97.4%	30 Day FU: 97.2% 1 Year FU: 98.1%



ITT= Intention-to-Treat population

PORTICO IDE Trial Enrollment

PORTICO IDE CLINICAL TRIAL with FlexNav™

Top 10 enrolling sites:

Site #	Co PI – Interv Cardiologist	Co PI- Cardiac Surgeon	Investigational Site	Subjects
1	Raj Makkar, MD	Wen Cheng, MD	Cedars-Sinai Medical Center, CA	137
2	Ron Waksman, MD	Paul Corso, MD	Washington Hospital Center, DC	66
3	William Abernethy, MD	Mark Groh, MD	Mission Health & Hospital, NC	49
4	Mark Cohen, MD	Mark Russo, MD	Newark Beth Israel Medical Center, NJ	50
5	James Hermiller, MD	David Heimansohn, MD	St. Vincent Hospital, IN	37
6	Stephen Worthley, MD	Joe Montarello, MD (2nd IC)	Royal Adelaide Hospital, AUS	29
7	Gerald Yong, MD	Sharad Shetty, MD (2nd IC)	Fiona Stanley Hospital, AUS	26
8	Neal Kleiman, MD	Michael Reardon, MD	Houston Methodist Hospital, TX	26
9	Chehab Bassem, MD	Brett Grizzell, MD	Cardiovascular Research Institute of Kansas, KS	25
10	Ray Matthews, MD	Vaughn Starnes, MD	Keck Medical Center of USC, CA	24

Note: Total N of enrolled subjects per site includes FlexNav DS cohort subjects

Pivotal RCT: Baseline Demographics

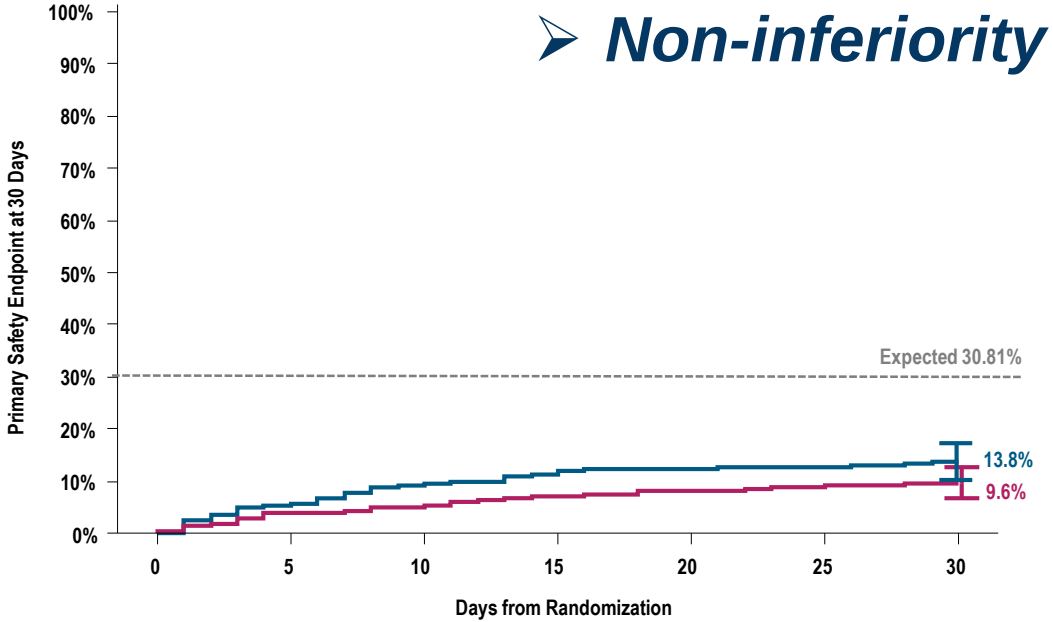
PORTICO IDE CLINICAL TRIAL

Characteristic	Portico valve (N=381)	Commercial valve (N=369)
Age, years	83.0 ± 7.6	83.7 ± 7.0
Female, %	52.0%	53.4%
STS Predicted Risk of Mortality, %	6.4%	6.6%
Extreme Risk, %	18.4%	17.1%
NYHA Class III/IV, %	71.4%	72.9%
Prior Stroke	7.6%	13.3%
PTCA with Stent	28.3%	29.0%
Atrial Fibrillation	32.8%	39.3%
Prior PPM	15.0%	17.1%
Diabetes Mellitus, %	37.5%	38.5%
Kidney Disease	25.2%	25.5%
Pulmonary Hypertension, %	34.4%	34.1%
≥1 Frailty Factor	93.4%	93.8%
AVA, cm^2	0.69 ± 0.18	0.67 ± 0.16
Mean Gradient, mmHg	46.2 ± 11.2	45.9 ± 11.9

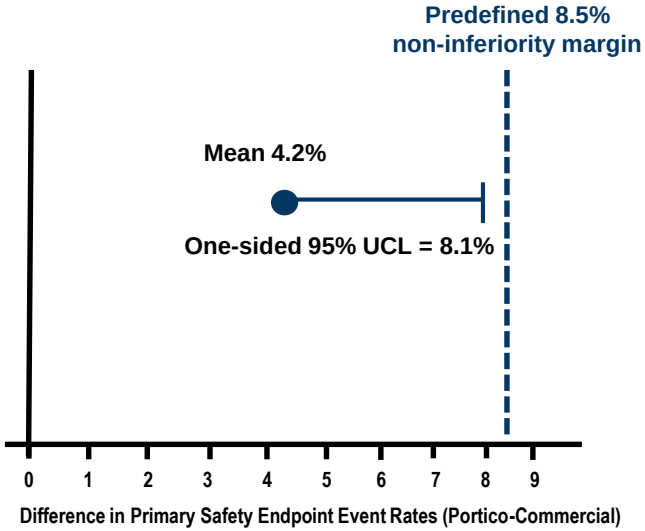
Pivotal RCT: Primary Safety Endpoint

PORTICO IDE CLINICAL TRIAL

➢ ***Non-inferiority met***



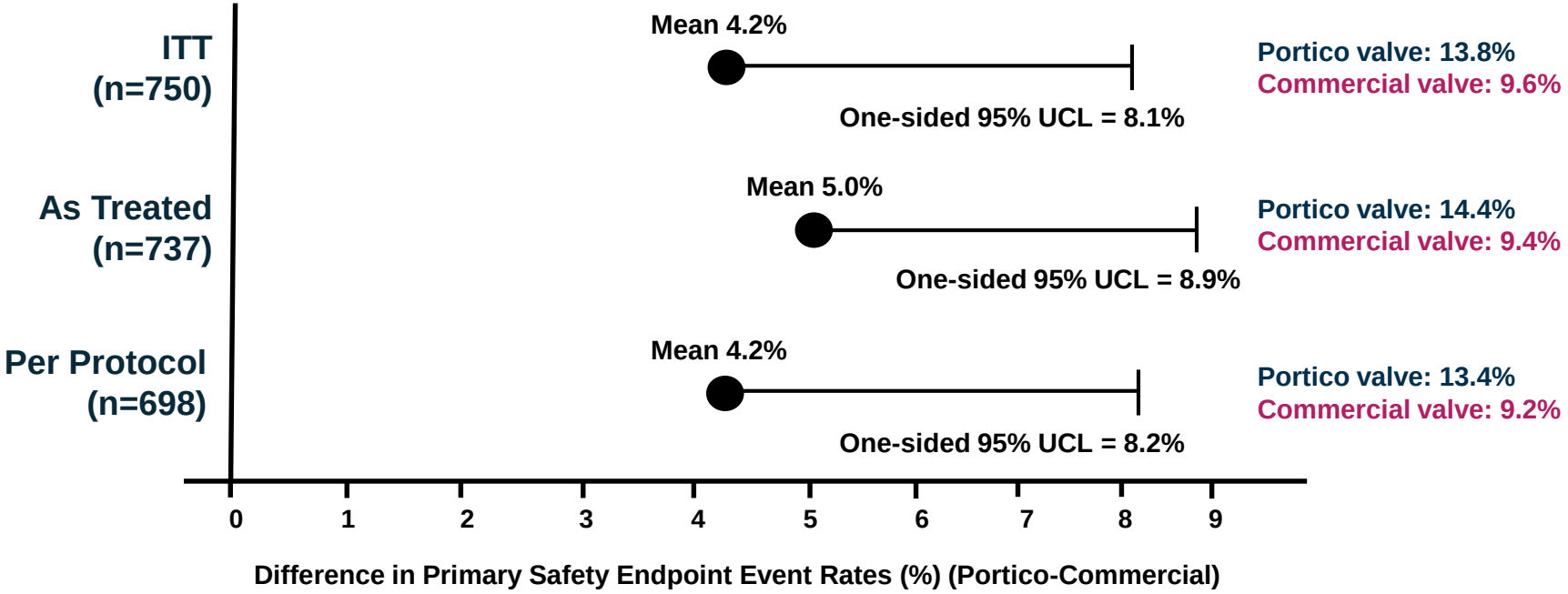
# At Risk							
Portico valve	381	357	342	333	329	327	321
Commercial valve	369	349	346	338	333	331	328



***P*-value for non-inferiority = 0.03**

Pivotal RCT: Additional Safety Analyses

PORTICO IDE CLINICAL TRIAL



Pivotal RCT: Primary Safety Components

PORTICO IDE CLINICAL TRIAL

Clinical Endpoint at 30 Days	Portico valve N=381	Commercial valve N=369
All-Cause Mortality	3.5% (13)	1.9% (7)
Disabling Stroke	1.6% (6)	1.1% (4)
Life Threatening Bleeding Requiring Transfusion	4.5% (17)	3.6% (13)
Acute Kidney Injury Requiring Dialysis	1.1% (4)	0.8% (3)
Major Vascular Complications	9.6% (36)	6.3% (23)

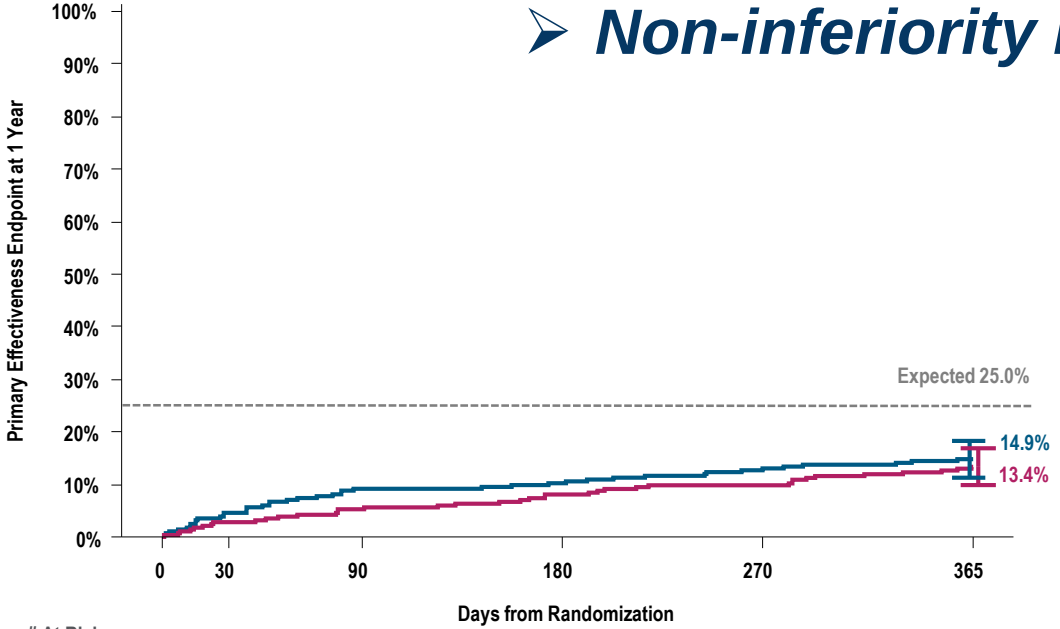
Data presented as Kaplan-Meier Estimate Event Rates % (n of subjects with event)

Difference in safety profiles driven by higher N of major vascular complications in Portico valve group (+3.3%).

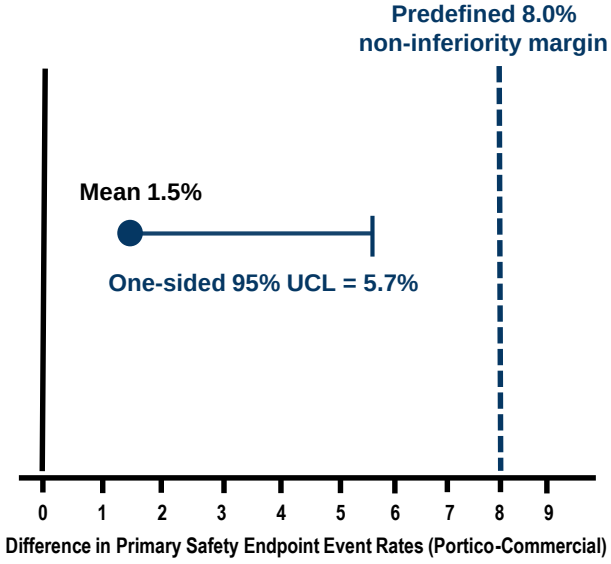
Pivotal RCT: Primary Effectiveness Endpoint

PORTICO IDE CLINICAL TRIAL

➢ ***Non-inferiority met***



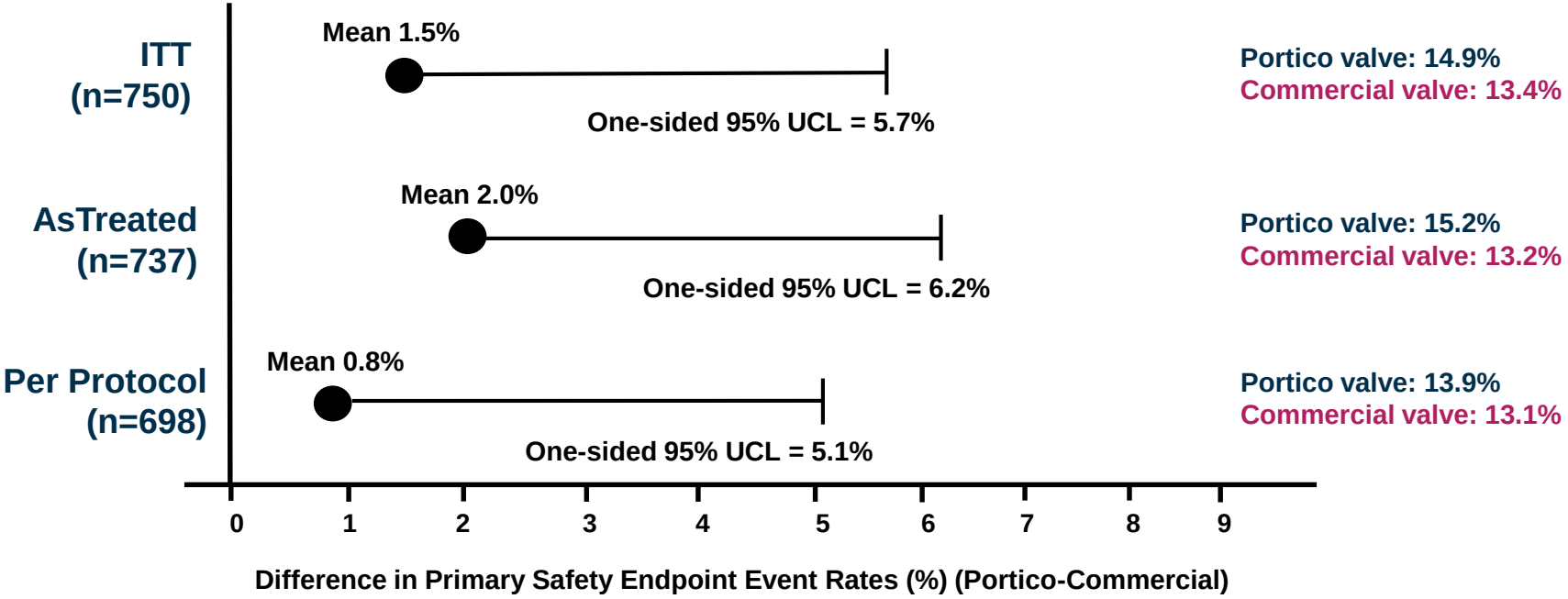
# At Risk						
Portico valve	381	355	335	330	319	300
Commercial valve	369	353	342	330	319	296



***P*-value for non-inferiority = 0.006**

Pivotal RCT: Additional Effectiveness Analyses

PORTICO IDE CLINICAL TRIAL

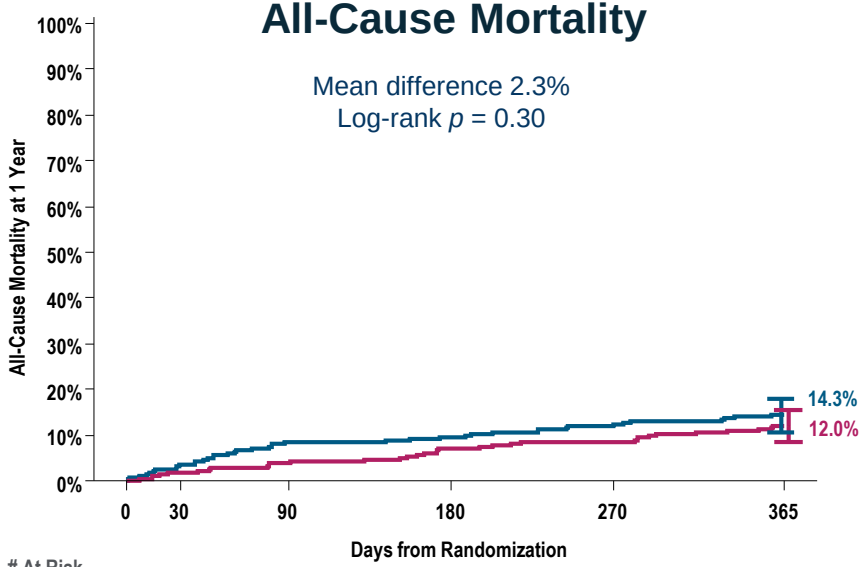


Pivotal RCT: Primary Effectiveness Components

PORTICO IDE CLINICAL TRIAL

All-Cause Mortality

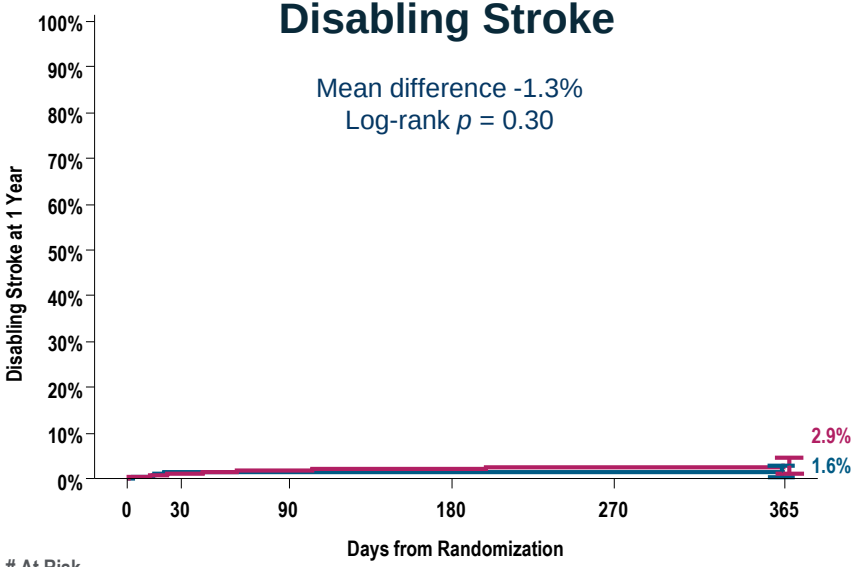
Mean difference 2.3%
Log-rank p = 0.30



# At Risk						
Portico valve	381	360	338	333	320	301
Commercial valve	369	356	347	335	324	300

Disabling Stroke

Mean difference -1.3%
Log-rank p = 0.30

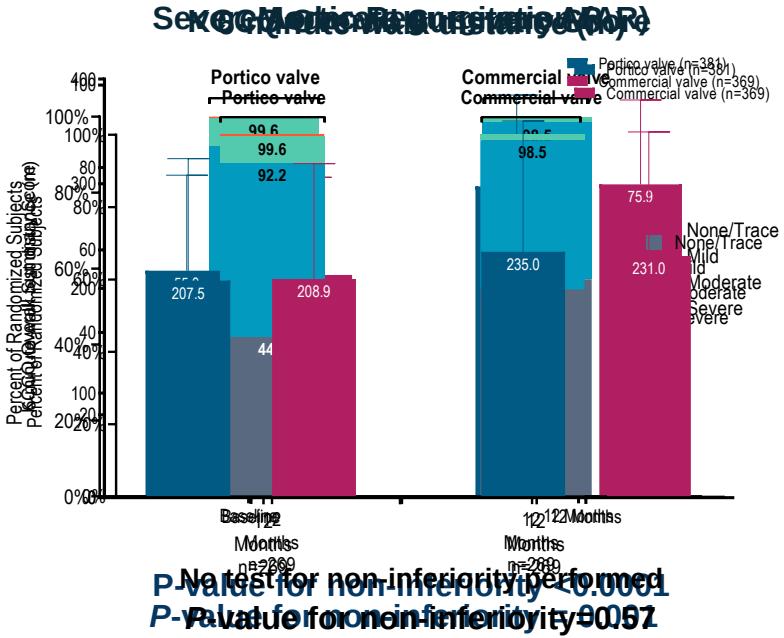


# At Risk						
Portico valve	381	355	335	330	319	300
Commercial valve	369	353	342	330	319	296

Pivotal RCT: Secondary Endpoints

PORTICO IDE CLINICAL TRIAL

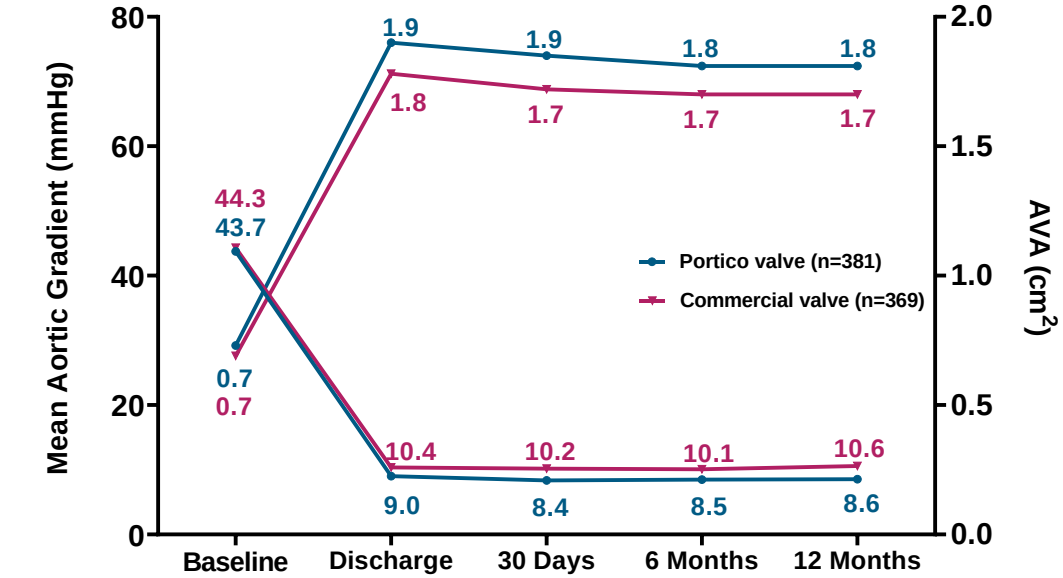
Endpoint at 1 Year	Portico valve (N=381)	Commercial valve (n=369)	One-sided 95% UCL/ LCL	Non-inferiority margin
Severe AR	0.4% (1/269)	0.0% (0/269)	2.34%	4%
KCCQ-OS Score	75.4 (274)	75.9 (283)	-3.5	-10 points
Moderate or severe AR	7.8% (21/269)	1.5% (4/269)	9.24%	6%
6-minute walk distance (m)	235.0 (227)	231.5 (225)	-15.4	-36 m



No test for non-inferiority performed

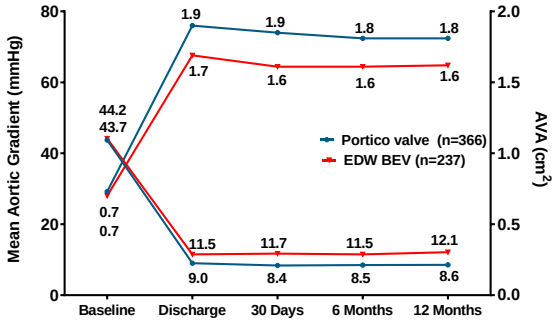
Pivotal RCT: Valve Hemodynamics

PORTICO IDE CLINICAL TRIAL

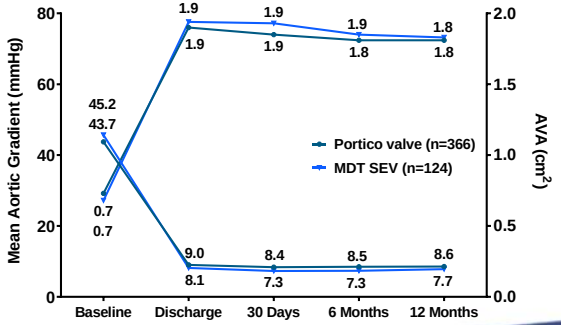


	Baseline	Discharge	30 Days	6 Months	12 Months
Mean Gradient					
Portico valve	372	360	337	298	274
Commercial valve	357	346	340	297	273
AVA					
Portico valve	349	327	321	276	252
Commercial valve	341	326	317	279	262

Portico valve Vs. EDW



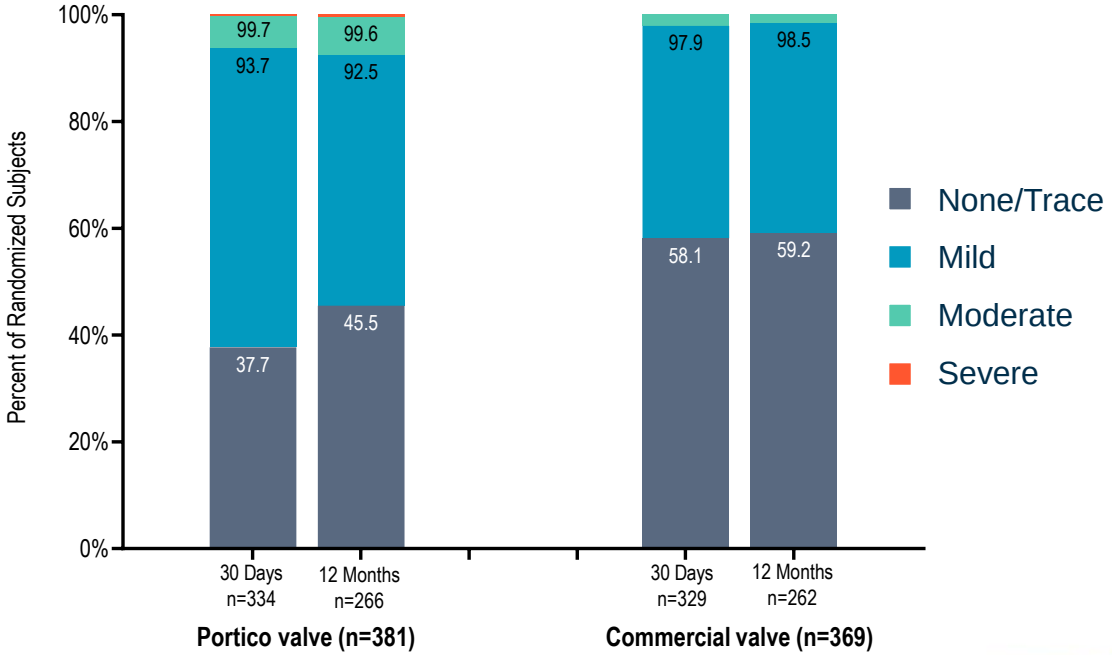
Portico valve Vs. MDT



Pivotal RCT: Paravalvular Leak

PORTICO IDE CLINICAL TRIAL

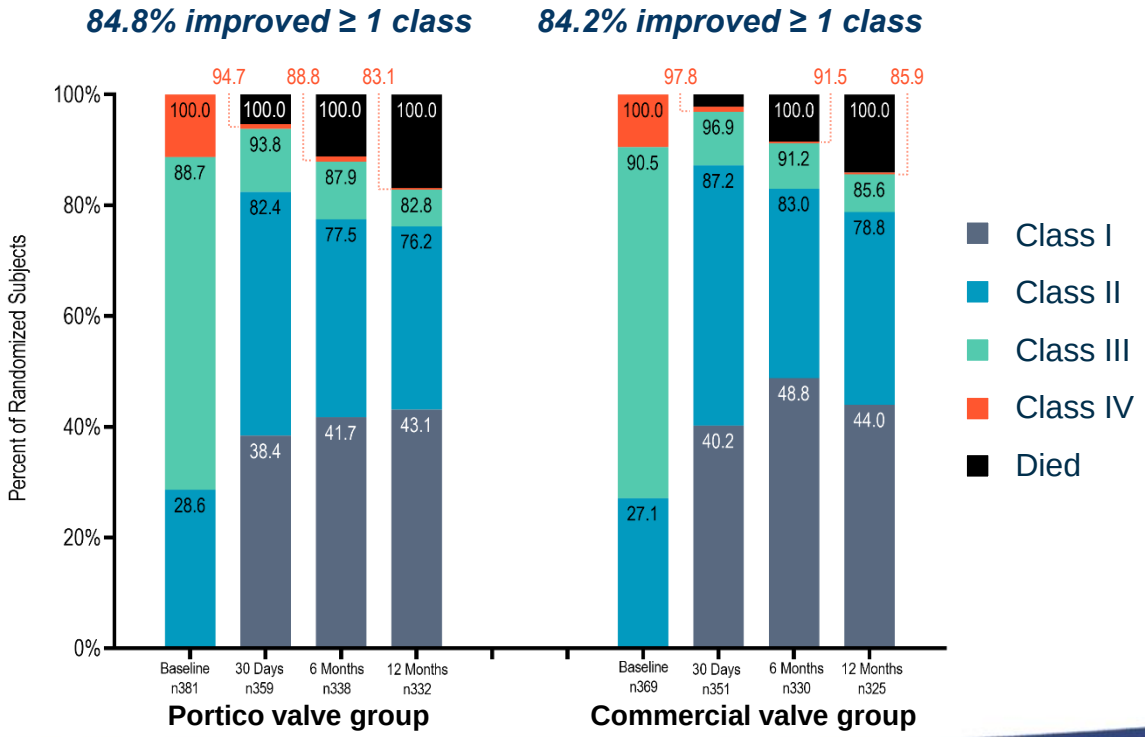
- Moderate or greater PVL is higher in Portico valve group
- 63% of all commercial valves implanted had a PVL reducing feature



Pivotal RCT: NYHA Functional Status

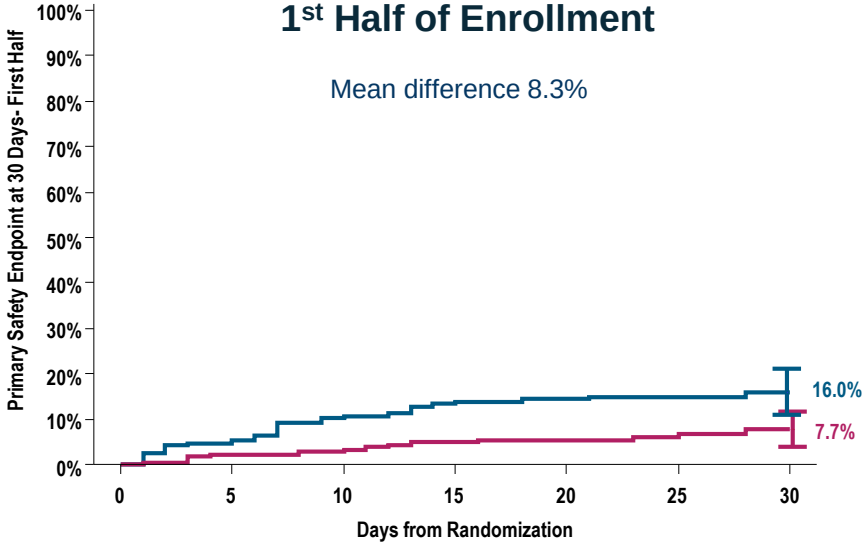
PORTICO IDE CLINICAL TRIAL

Both groups experienced similar improvements in cardiac symptoms (improved ≥1 NYHA class) at 1 year

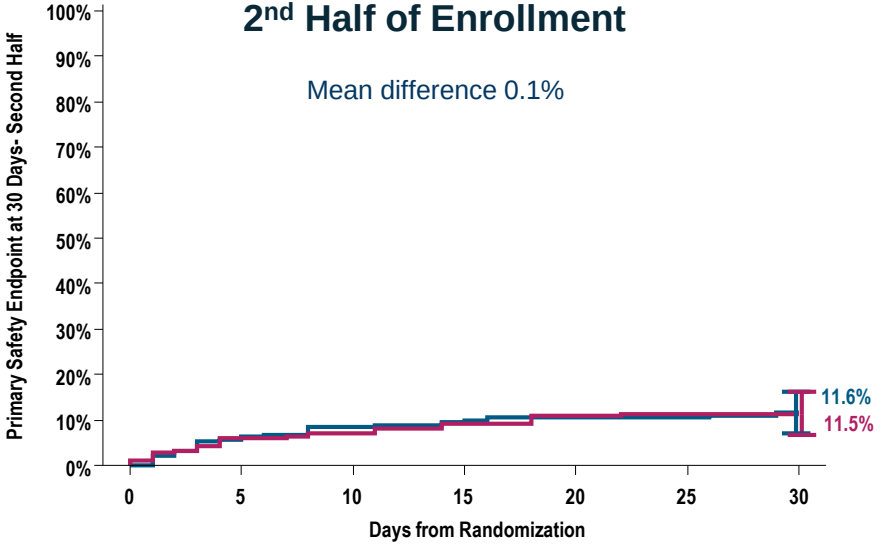


Pivotal RCT: Post Hoc Learning Analysis
Primary Safety Endpoint

PORTICO IDE CLINICAL TRIAL



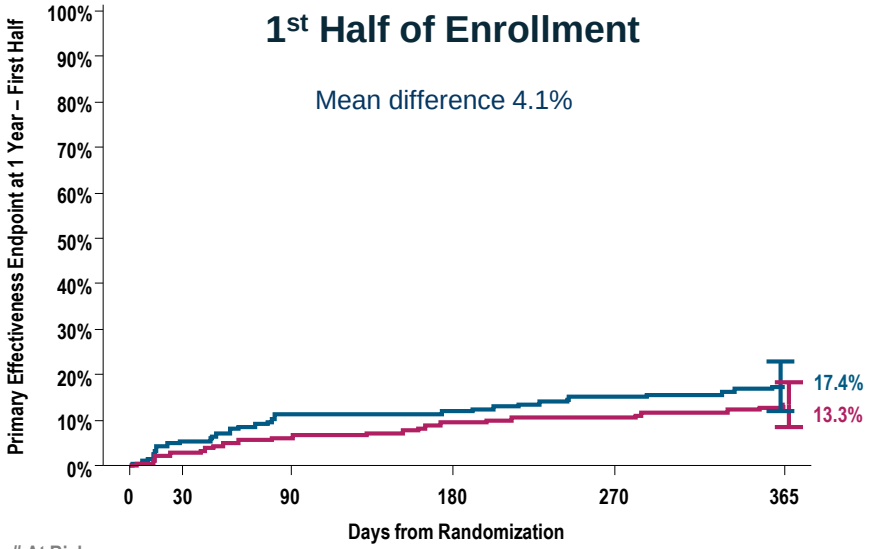
# At Risk							
Portico valve	191	178	168	161	159	158	156
Commercial valve	184	178	177	173	172	171	168



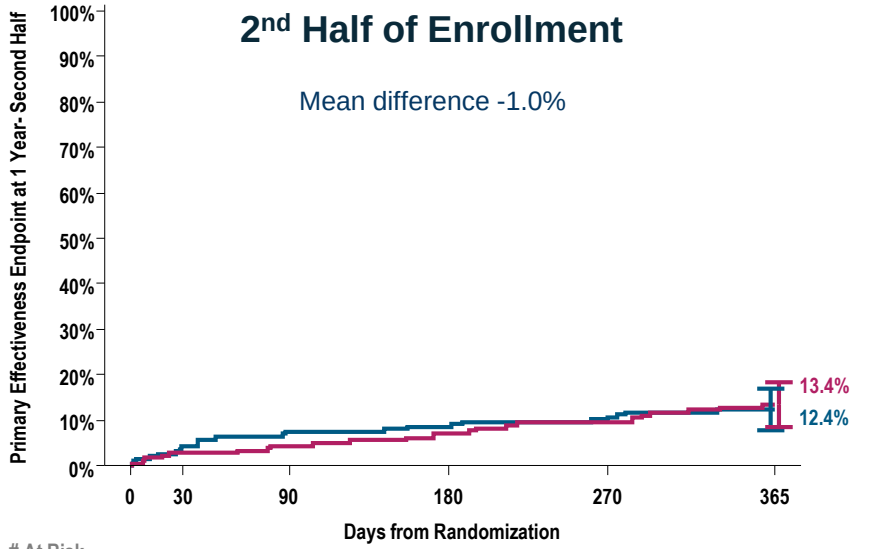
# At Risk							
Portico valve	190	179	174	172	170	169	165
Commercial valve	185	171	169	165	161	160	160

Pivotal RCT: Post Hoc Learning Analysis
Primary Effectiveness Endpoint

PORTICO IDE CLINICAL TRIAL



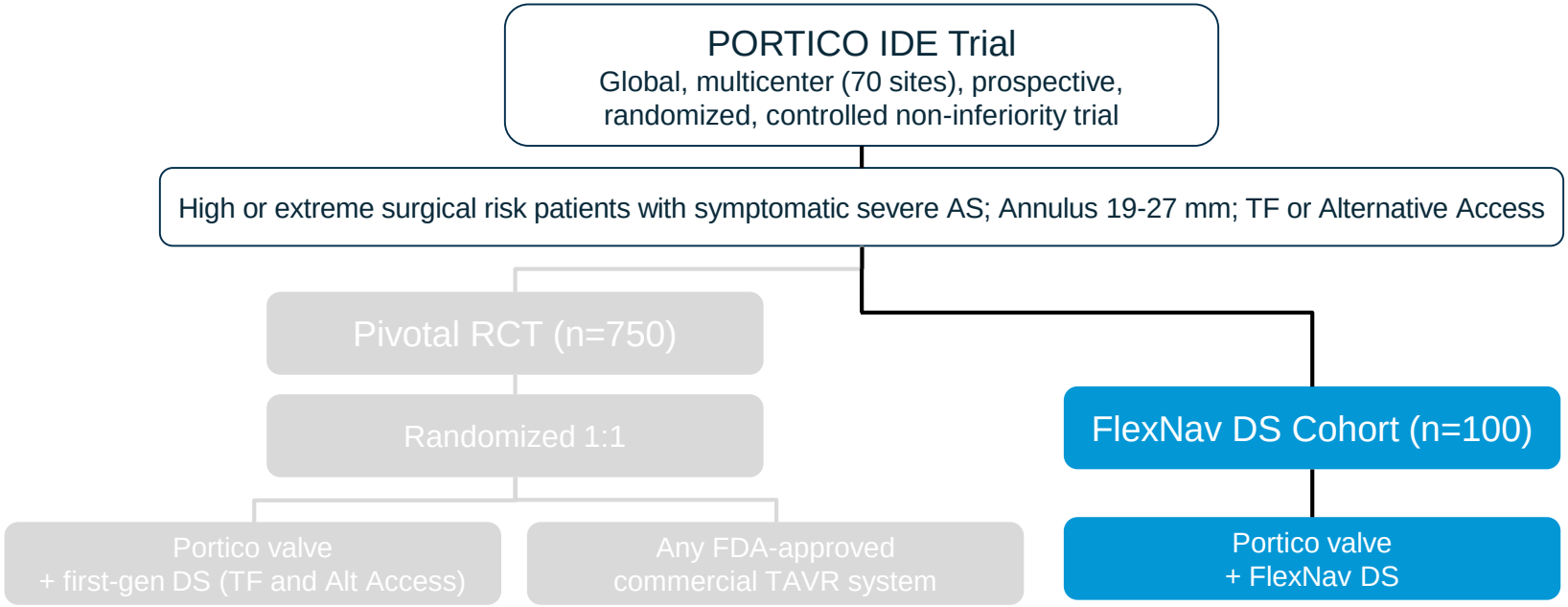
# At Risk						
Portico valve	191	176	164	161	154	149
Commercial valve	184	177	170	163	158	152



# At Risk						
Portico valve	190	179	171	169	165	151
Commercial valve	185	176	172	167	161	144

PORTICO IDE Trial Design

PORTICO IDE CLINICAL TRIAL with FlexNav™



Portico™ vs FlexNav™ Delivery System

PORTICO IDE CLINICAL TRIAL

with FlexNav™

Portico Delivery System

- 18-19 French
- Pioneered ability to recapture, reposition, and retrieve
- Flexible capsule

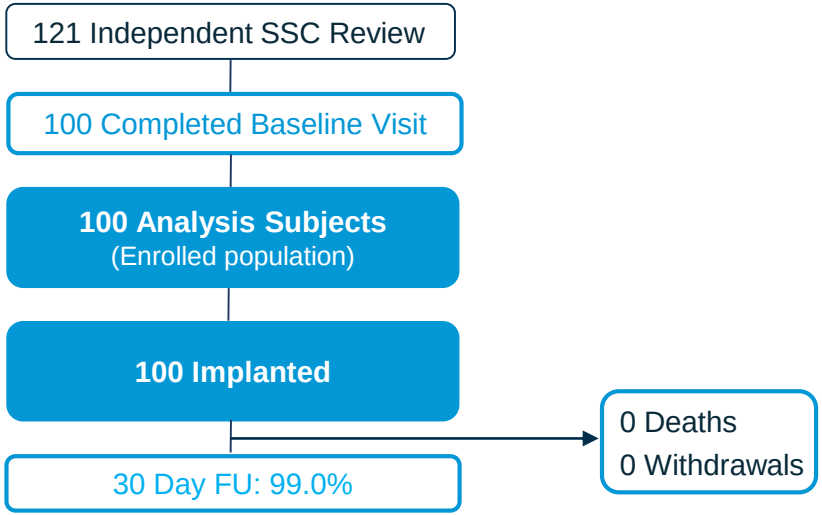
FlexNav Delivery System

- 14-15 French equivalent
- Stability layer for accurate placement
- Integrated sheath
- Hydrophilic coating
- Redesigned handle

FlexNav DS Cohort: Patient Flow

PORTICO IDE CLINICAL TRIAL with FlexNav™

100 analysis subjects enrolled from 23 sites in US, AUS and EU between Nov 2018 and Jun 2019



Note: Eligibility criteria, study oversight, study assessments and follow-up schedule same as pivotal RCT

FlexNav DS Cohort: Endpoint

PORTICO IDE CLINICAL TRIAL with FlexNav™

Primary Endpoint: VARC 2 defined major vascular complications at 30 days

Analysis Population:	*All subjects that had the FlexNav DS inserted into the vasculature*

FlexNav DS Cohort: Baseline Demographics

PORTICO IDE CLINICAL TRIAL with FlexNav™

Characteristic	RCT Portico valve N=381	RCT Commercial valve N=369	FlexNav DS Cohort N=100
Age, years	83.0 ± 7.6	83.7 ± 7.0	85.2 ± 5.7
Female, %	52.0%	53.4%	60.0%
STS Predicted Risk of Mortality, %	6.4%	6.6%	5.0%*
Extreme Risk, %	18.4%	17.1%	20.0%
NYHA Class III/IV, %	71.4%	72.9%	65.0%
Prior Stroke	7.6%	13.3%	11.0%
Atrial Fibrillation	32.8%	39.3%	29.0%
Prior PPI	15.0%	17.1%	11.0%
Pulmonary Hypertension	34.4%	34.1%	40.0%
≥ 1 Frailty Factor	93.4%	93.8%	97.0%
AVA, cm^2	0.69 ± 0.18	0.67 ± 0.16	0.68 ±0.18
Mean Gradient, mmHg	46.2 ± 11.2	45.9 ± 11.9	45.1 ± 13.3

* New STS risk calculator introduced Nov 15, 2018

FlexNav DS Cohort: Clinical Outcomes at 30 Days

PORTICO IDE CLINICAL TRIAL with FlexNav™

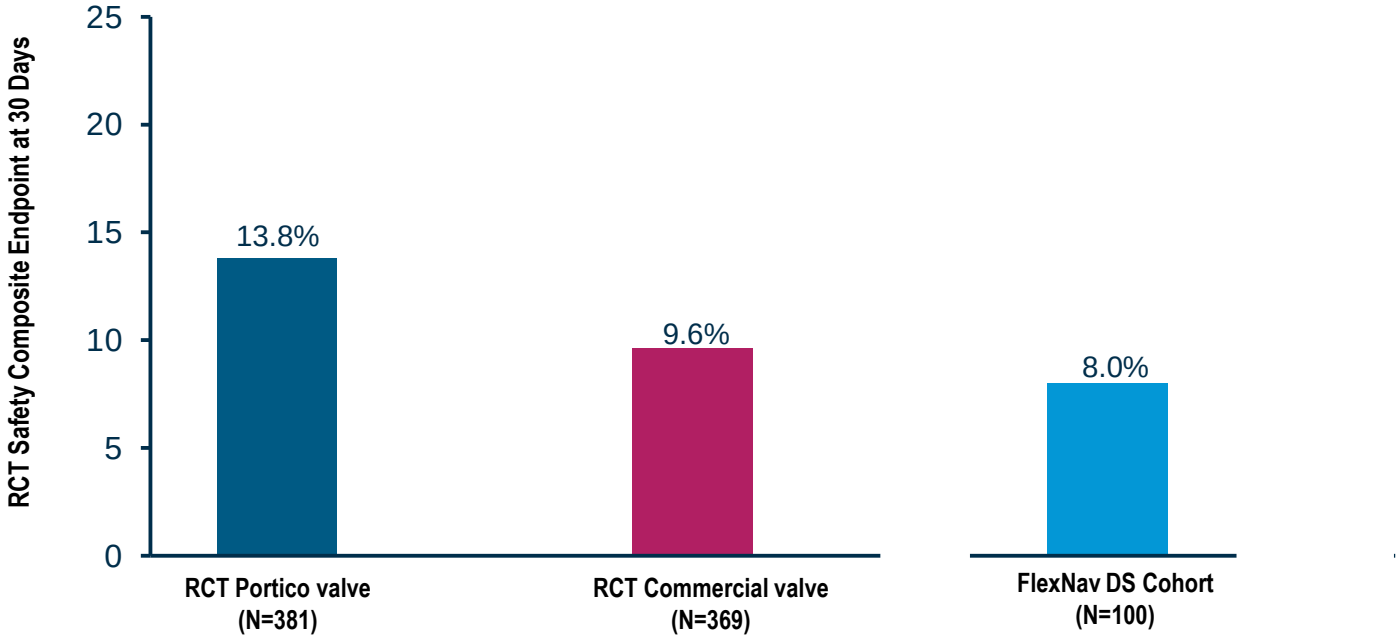
Primary endpoint: 7% major vascular complications

VARC 2 Endpoint	RCT Portico valve N=381	RCT Commercial valve N=369	FlexNav DS Cohort N=100
All-Cause Mortality	3.5%	1.9%	**0.0%**
Cardiovascular Mortality	3.2%	1.7%	**0.0%**
Disabling Stroke	1.6%	1.1%	**0.0%**
Life-Threatening Bleeding Requiring Transfusion	4.5%	3.6%	**4.0%**
Acute Kidney Injury Requiring Dialysis	1.1%	0.8%	**0.0%**
Major Vascular Complications	9.6%	6.3%	**7.0%**
New PPI	27.7%	11.6%	**14.6%**
Moderate or Greater PVL	6.3%	2.1%	**6.5%**

Data presented as Kaplan-Meier Estimate Event Rates % (n of subjects with an event)

Pivotal RCT + FlexNav DS Cohort: Safety Composite

PORTICO IDE CLINICAL TRIAL with FlexNav™



Summary

PORTICO IDE CLINICAL TRIAL with FlexNav™

- Trial met both safety and effectiveness endpoints
- Major vascular complications occurred with greater frequency in Portico valve group driving difference in safety profile
- Safety and effectiveness improved in the second half of the trial in Portico valve group
- Portico valve was associated with improved hemodynamics (larger valve areas and smaller gradients) but higher rate of moderate PVL compared to commercial valves
- FlexNav DS was associated with better overall safety profile
  - Fewer major vascular complications
  - No deaths or disabling strokes
  - Reduction in new permanent pacemaker implants

Limitations

PORTICO IDE CLINICAL TRIAL with FlexNav™

- Actual performance for both groups was better than assumed rates
- Over the 3.5 year enrollment period, multiple valve types and design iterations were introduced in the commercial valve group
- Implant experience with the Portico valve was disproportionate (median 5 implants per site, 6 sites >20 implants) relative to commercial valves
- FlexNav DS cohort is a relatively small, non-randomized cohort

Implications

PORTICO IDE CLINICAL TRIAL with FlexNav™

- Findings suggest the Portico valve may provide an additional transcatheter heart valve type to treat high and extreme risk patients with severe AS and help expand patient access to this potentially life-saving procedure
- Next-generation valve with design modifications to reduce PVL is currently being tested in clinical trials