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Update on TAVR Results 2014

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Mayo Clinic, Rochester

TCTAP 2014

Seoul, Korea

April 2014

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Presenter Disclosure Information

David R. Holmes, Jr., M.D.

"Update on TAVR Results 2014"

The following relationships exist related to this presentation:

None

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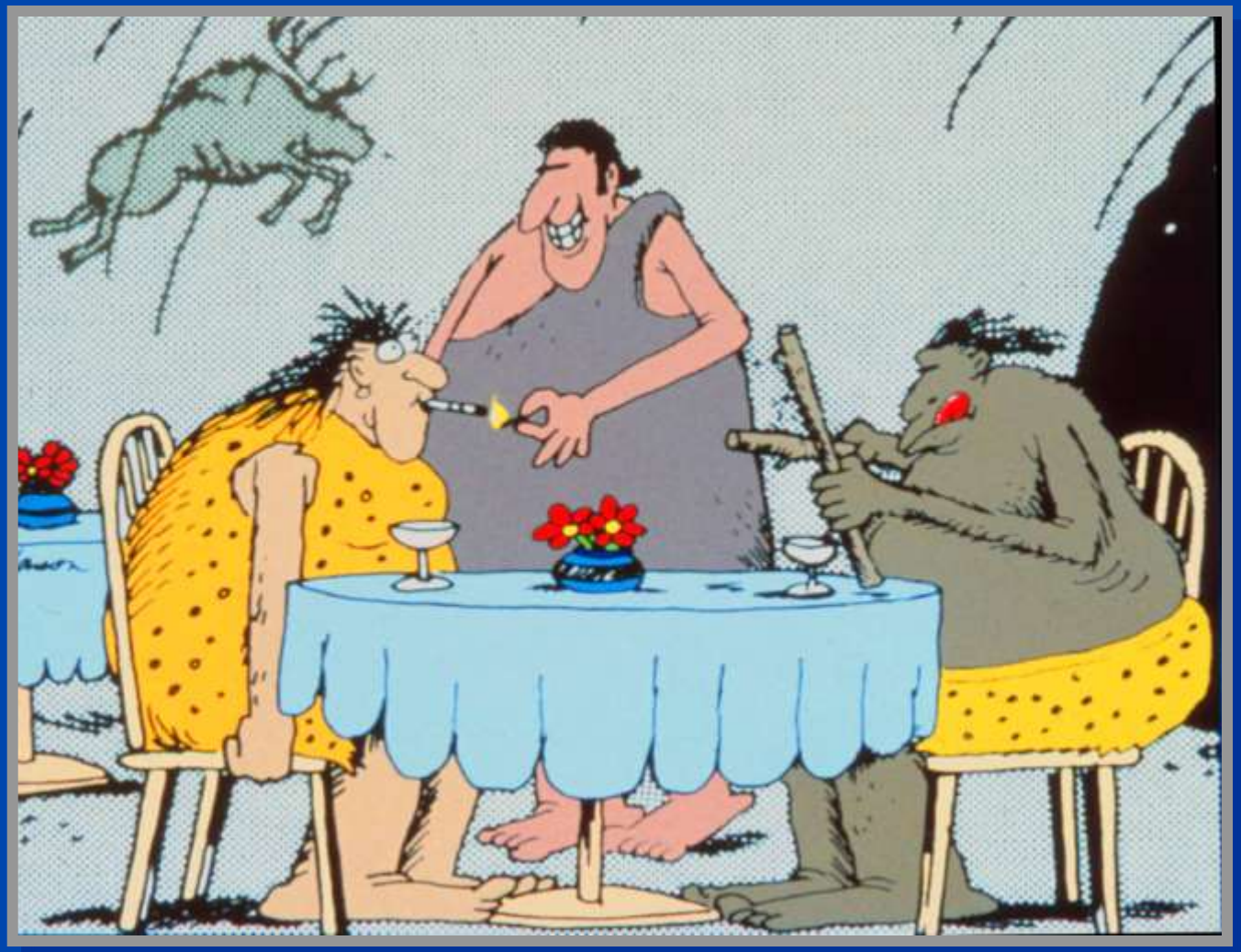
As Thak worked frantically to start a fire, a Cro-Magnon man, walking erect, approached the table and simply gave Theena a light.



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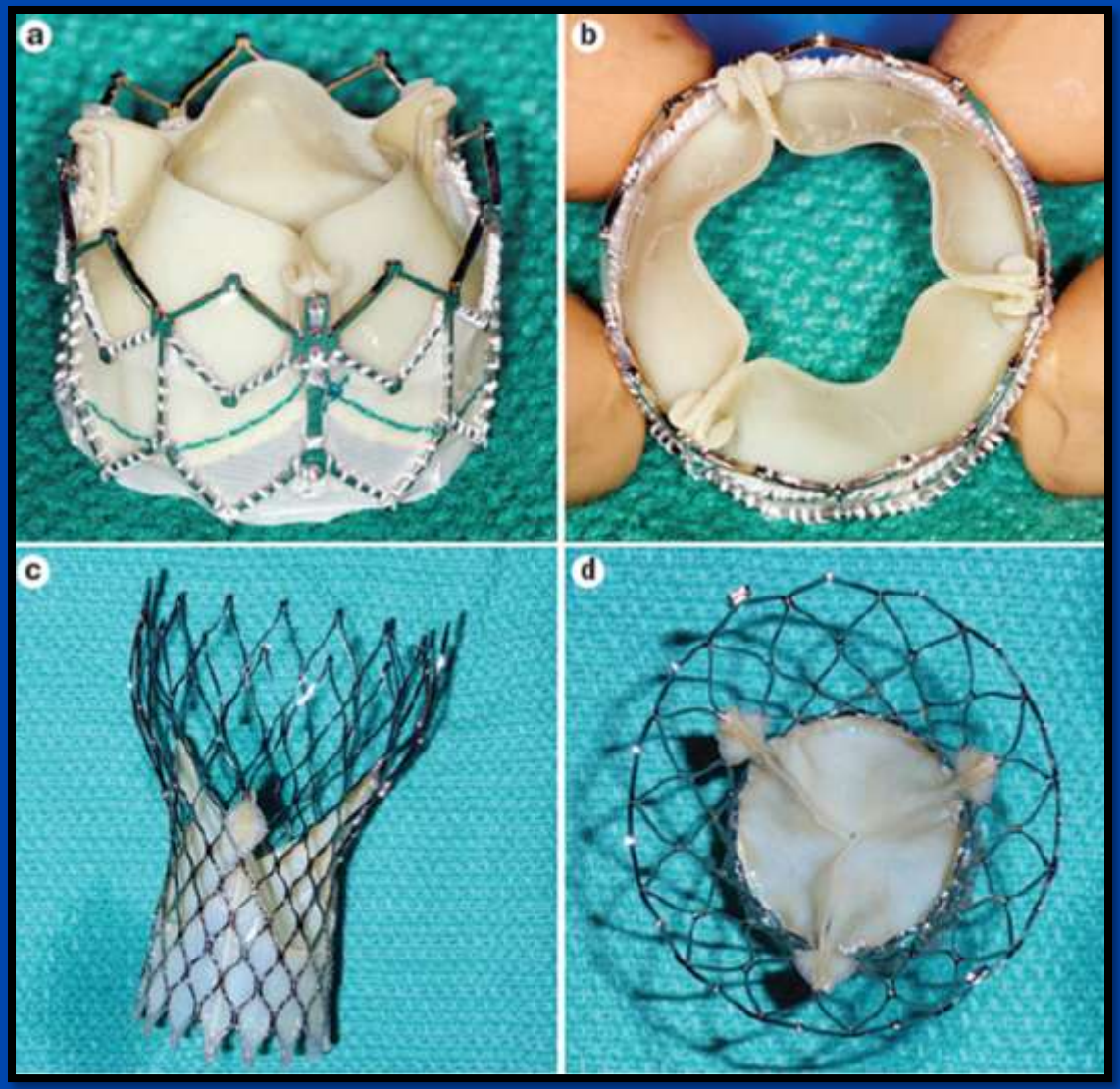
TAVI Valves Currently Used



A & B: Edwards SAPIEN XT®

C & D: 3rd Generation of the CoreValve®

Rodes-Cabau: Nat Rev Cardiol 9:15-29, 2012

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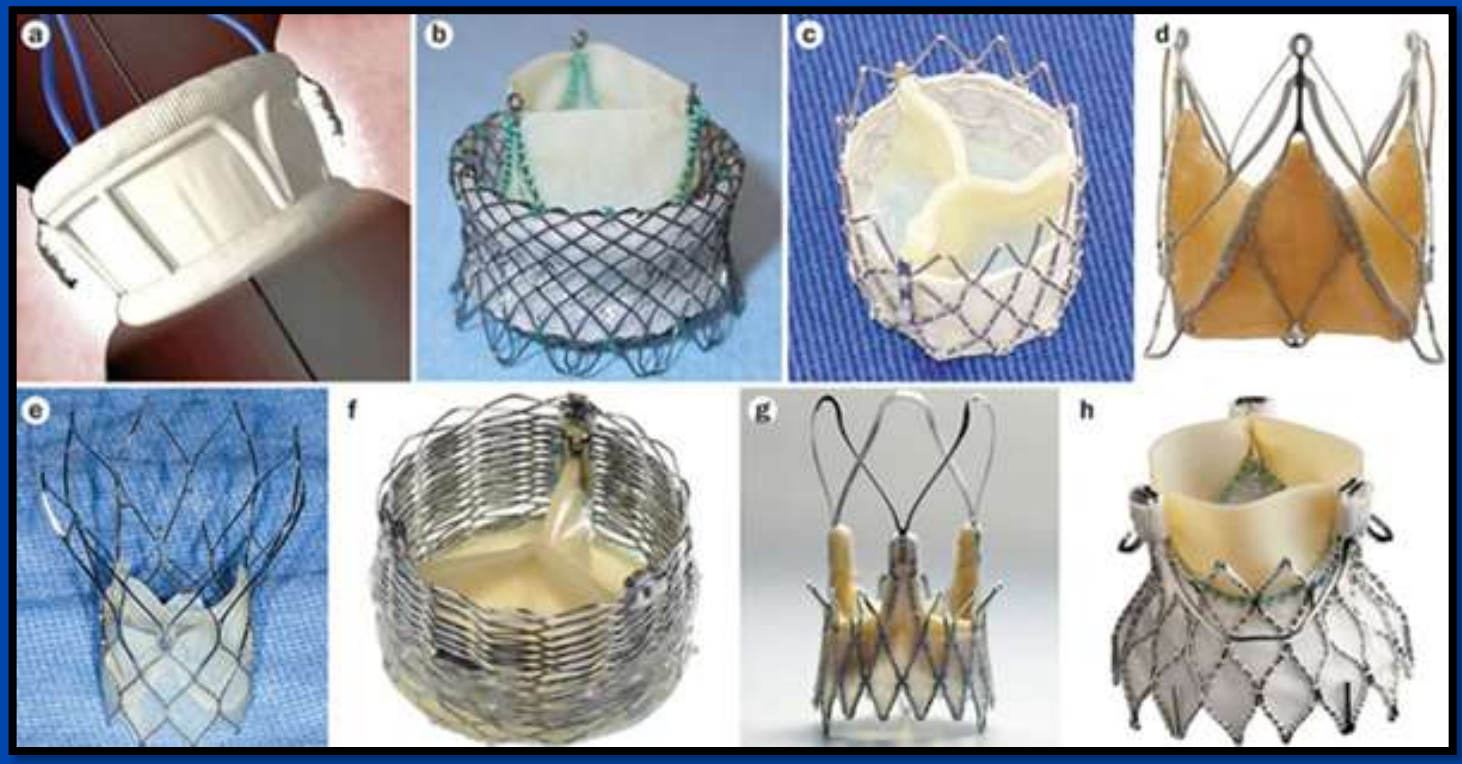
2nd Generation TAVI Devices

Direct Flow Medical® Valve (DFM)

Heart Leaflet Technologies (HLT)

Innovare Valve

JenaValve®



Portico® Valve

Sadra® Lotus Medical Valve

Symetis® Accurate Valve

Engager® Valve

Rodes-Cabau: Nat Rev Cardiol 9:15-29, 2012

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Background

- Transcatheter Aortic Valve Replacement (TAVR) is used with increasing frequency in patients with severe aortic stenosis (AS) who are at either high risk or extreme risk (inoperable) for conventional surgical aortic valve replacement (SAVR)

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Clinical Questions

1) What is the incidence of adverse clinical events of mortality, stroke and rehospitalization at 1 year post TAVR in the U.S.?
2) What is the average time alive and out of the hospital to 6 months?
3) Are there any striking associations between patient characteristics and clinical outcomes at 1 year post TAVR?

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Patient Population

- 5,980 Patients enrolled in the STS/ACC TVT registry November 2011 – July 2013
- Age > 65 years
- Medicare insurance
- Part A & B and non-HMO during month of index procedure
- Index admission linked to inpatient Medicare claims using direct patient identifiers (97% successful record linkage rate)

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Patient Characteristics

Characteristic	Study Cohort N= 5,980
Age (yr) Median (25th, 75th)	85 (79, 88)
75-84, n (%)	2,244 (37.5)
85-94, n (%)	2,869 (48.0)
Female, n (%)	3,006 (50.4)
STS PROM Score (25th, 75th)	7.1 (4.7, 10.9)
<8% n, (%)	3,405 (57.0)
8-15%	1,844 (30.8)
>15%	729 (12.2)
NYHA Class III/IV Heart Failure, n (%)	4,876 (83.6)
CAD, n (%)	3,564 (61.7)

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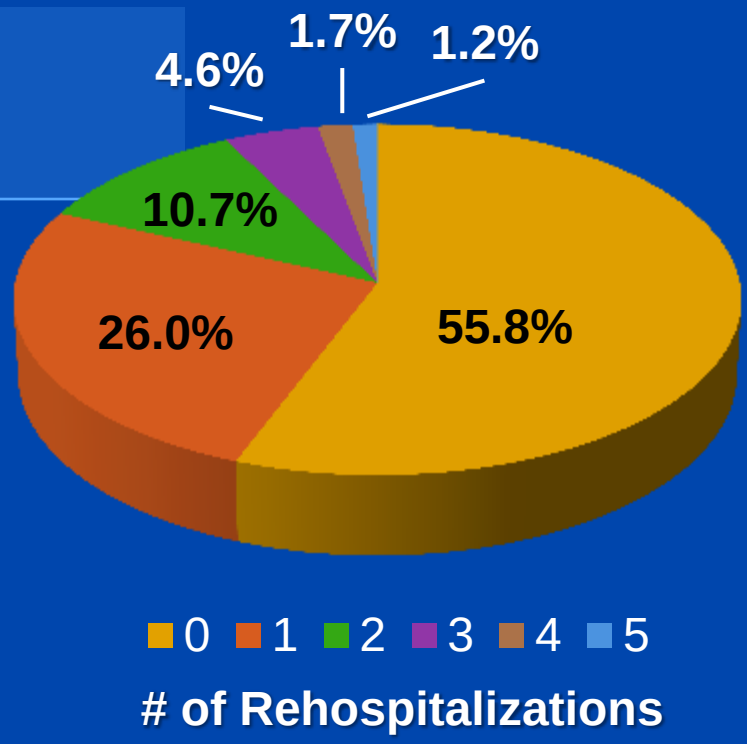
One Year Outcome

Mortality	26.2% (24.7%, 27.8%)
Stroke	3.6% (3.1%, 4.2%)
Death or stroke	28.4% (26.9%, 30.0%)
Incidence & frequency of repeat hospitalization within 6 months	



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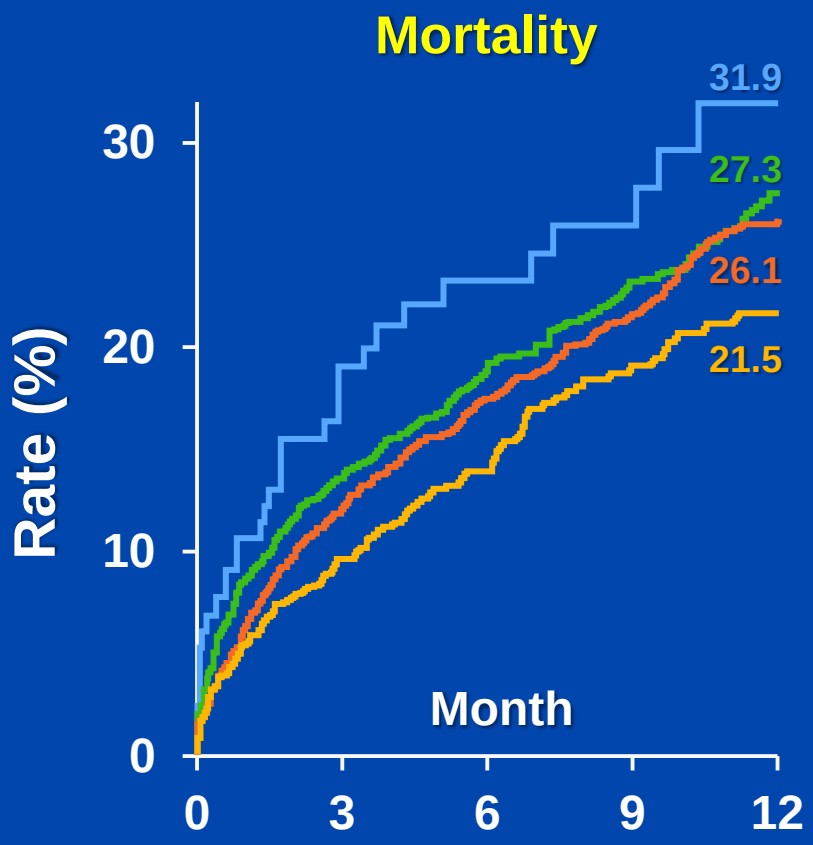
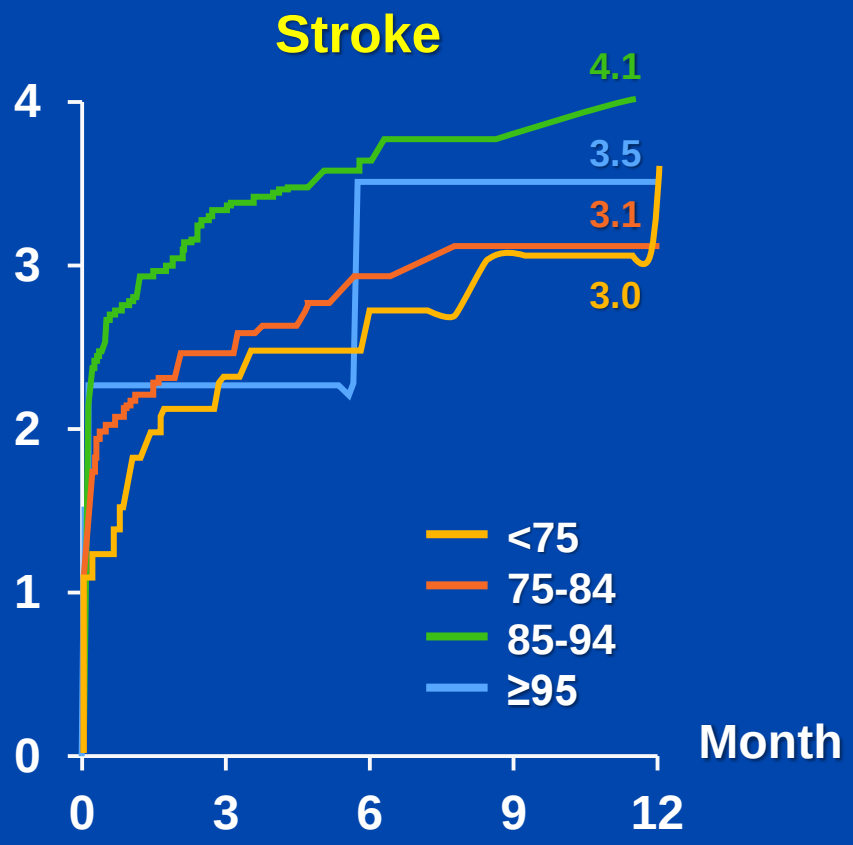
Cumulative Incidence of Death and Stroke
Affect of Age



	HR	P
75-84 vs <75	1.224	0.060
85-94 vs <75	1.359	0.006
95+ vs <75	1.648	0.016



	HR	P
75-84 vs <75	0.999	0.998
85-94 vs <75	1.160	0.613
95+ vs <75	0.289	0.247

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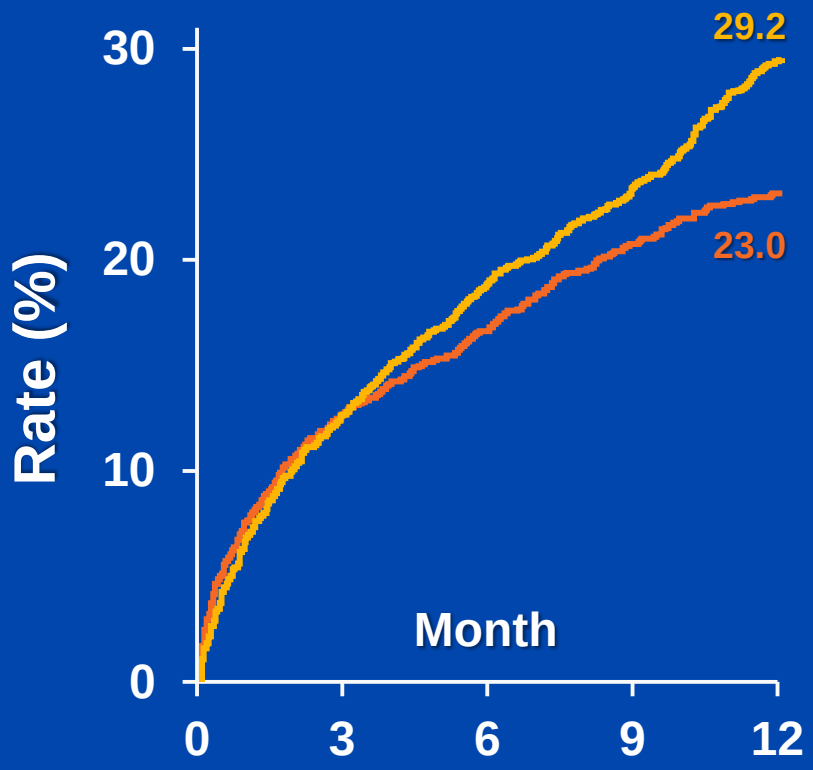
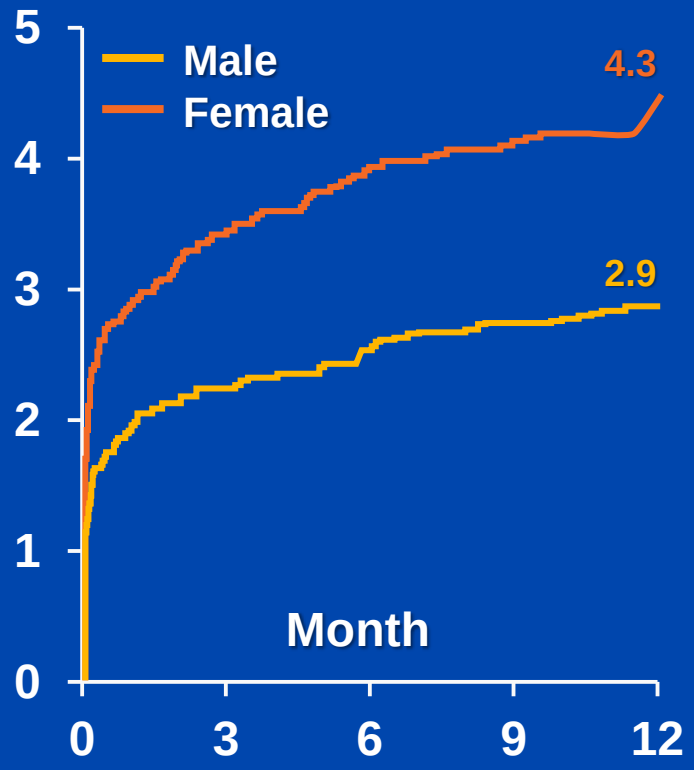
Cumulative Incidence of Death and Stroke
Affect of Sex

Mortality



	HR	P
Male vs Female	1.189	0.007

Stroke



	HR	P
Male vs Female	0.655	0.012

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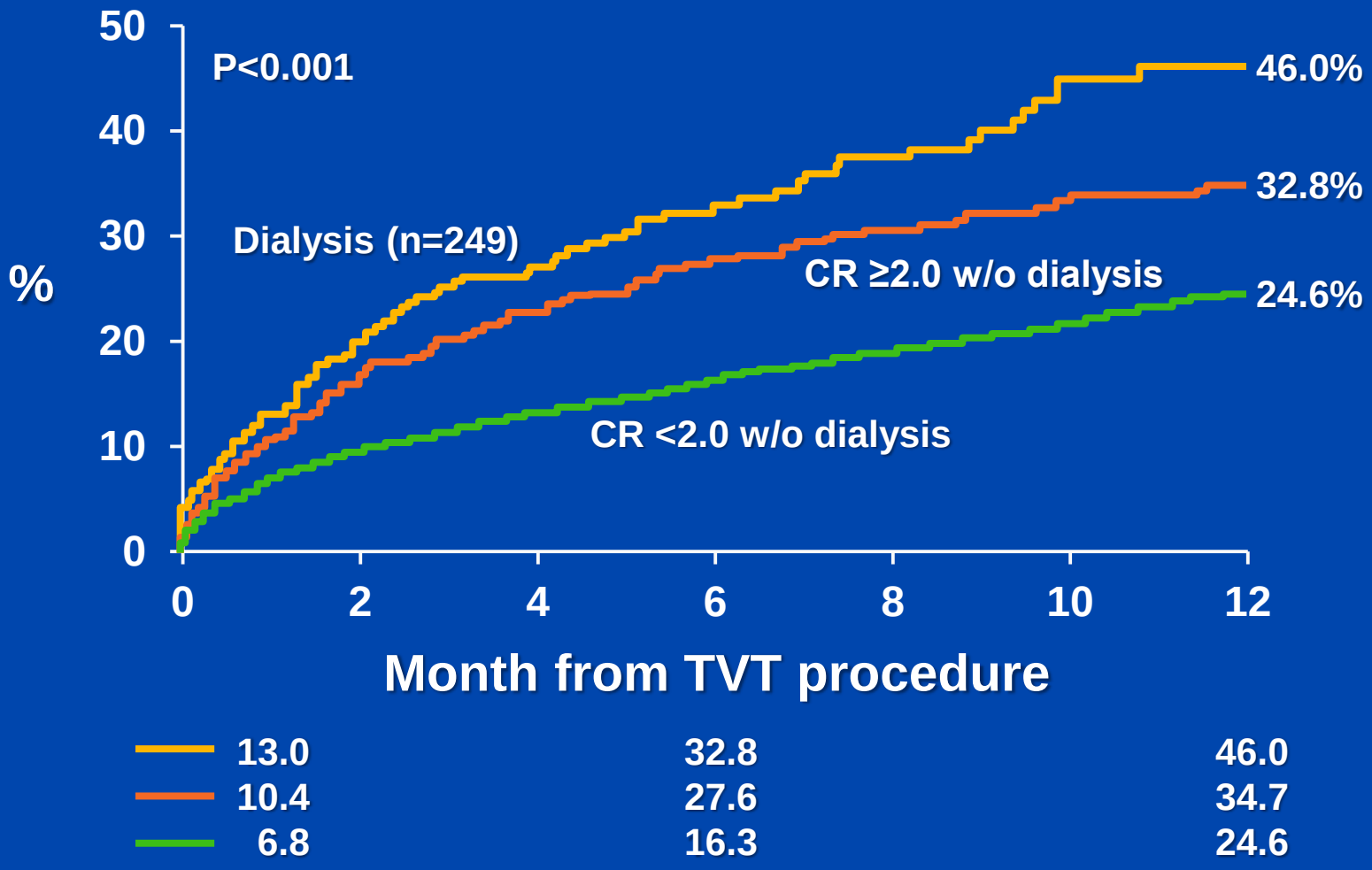
Mortality



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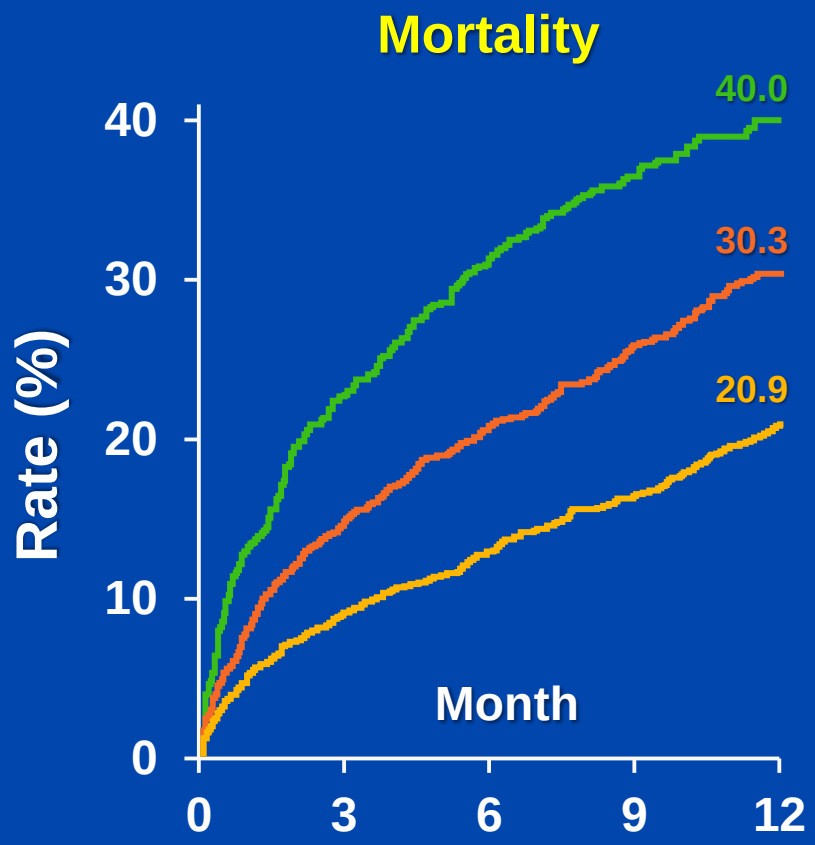
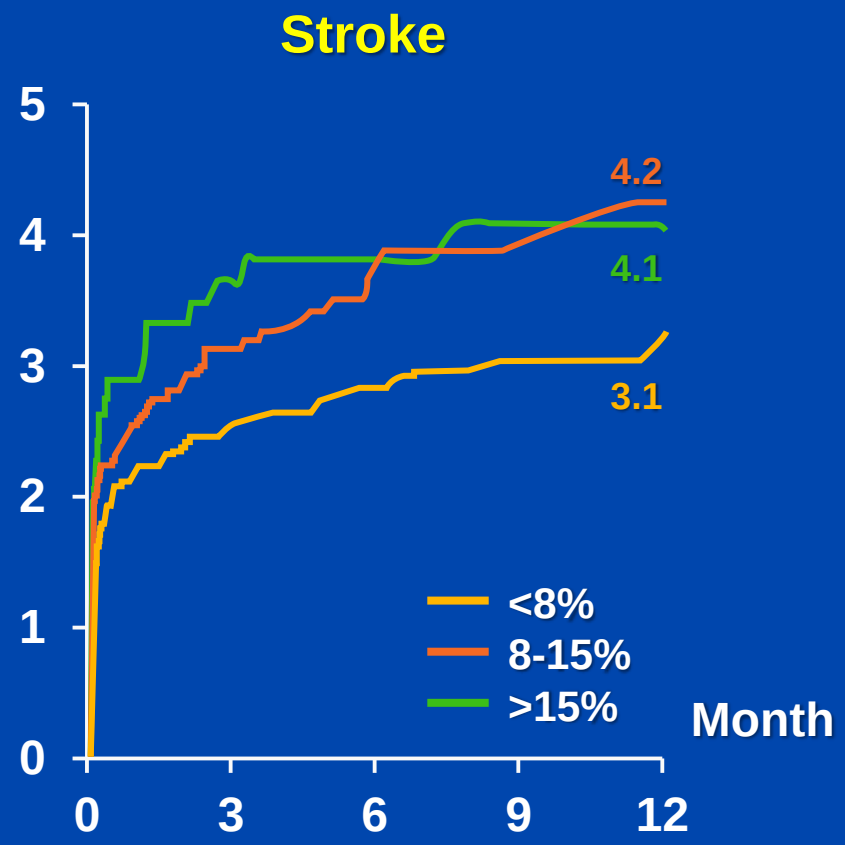
Cumulative Incidence of Death and Stroke
Affect of STS Prom



	HR	P
8-15 vs <8%	1.441	<0.001
>15 vs <8%	1.785	<0.001



	HR	P
8-15 vs <8%	1.037	0.855
>15 vs <8%	1.151	0.619

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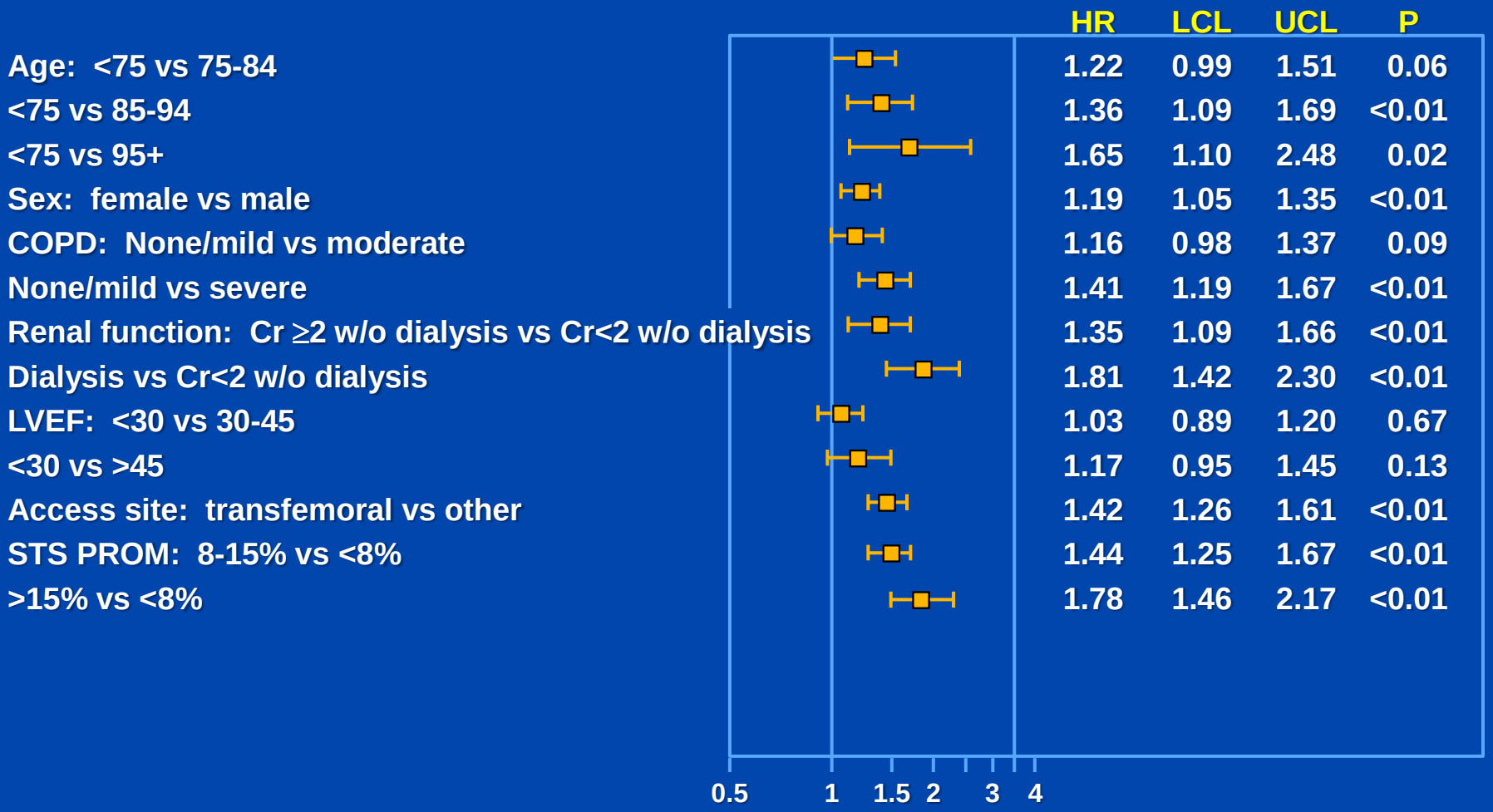
Multivariable Model of 1-Year Mortality after TAVR



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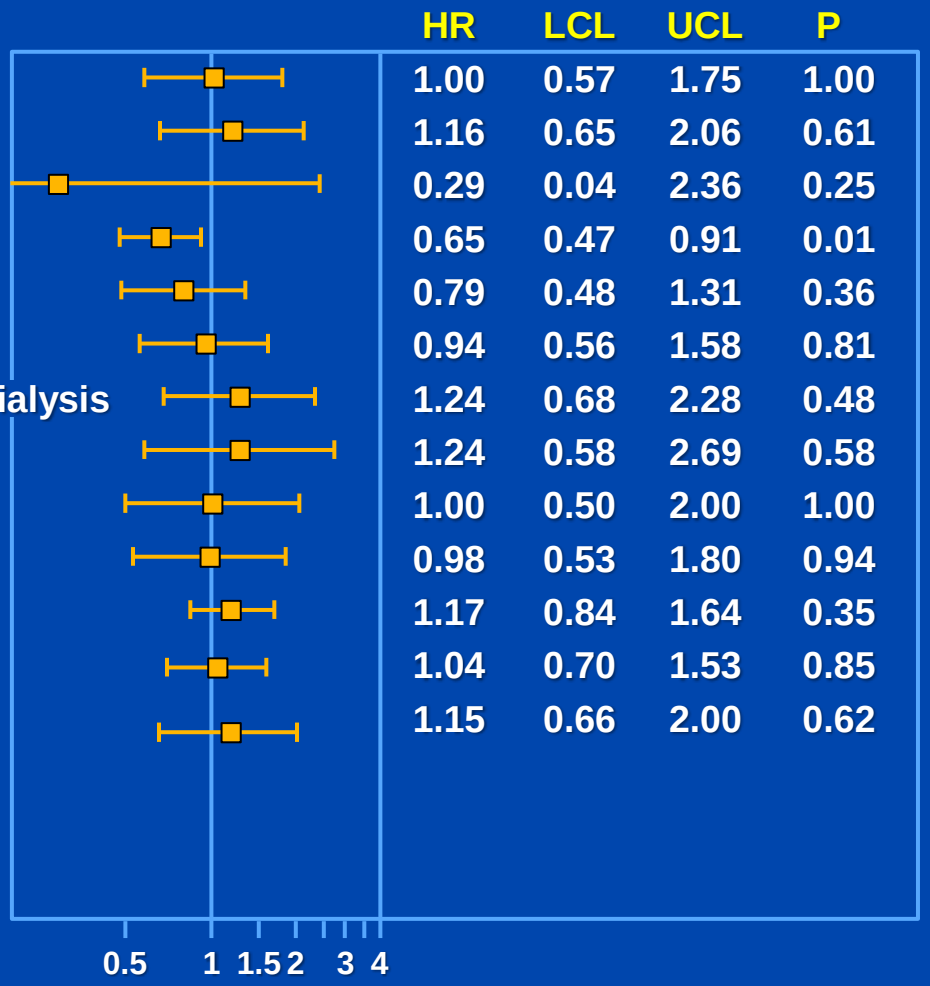
Multivariable Model of 1-Year Stroke after TAVR



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Conclusions (2)

- Different baseline demographics are significantly associated with 1 year mortality as compared with stroke

Mortality	Stroke
Age	Female gender
Male gender	
Severe COPD	
ESRD	
Access site	
STS PROM	

- Identification of these associations is essential for developing risk prediction models and will aid in patient selection criteria for TAVR

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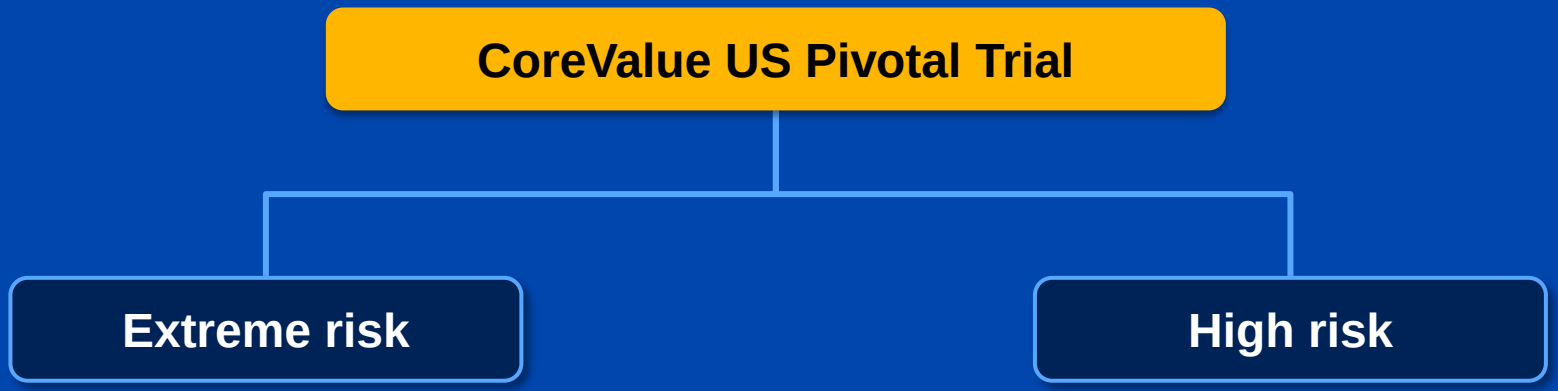
Extreme Risk Trial



TAVR with the self-expanding CoreValve prosthesis reduced the composite endpoint of death from any cause or major stroke at 1 year compared to a performance goal in symptomatic patients with severe aortic stenosis at extreme surgical risk

Popma JJ, Adams DH, Reardon MJ, et al: J Am Coll Cardiol 2014; March 19 (Epub ahead of print)

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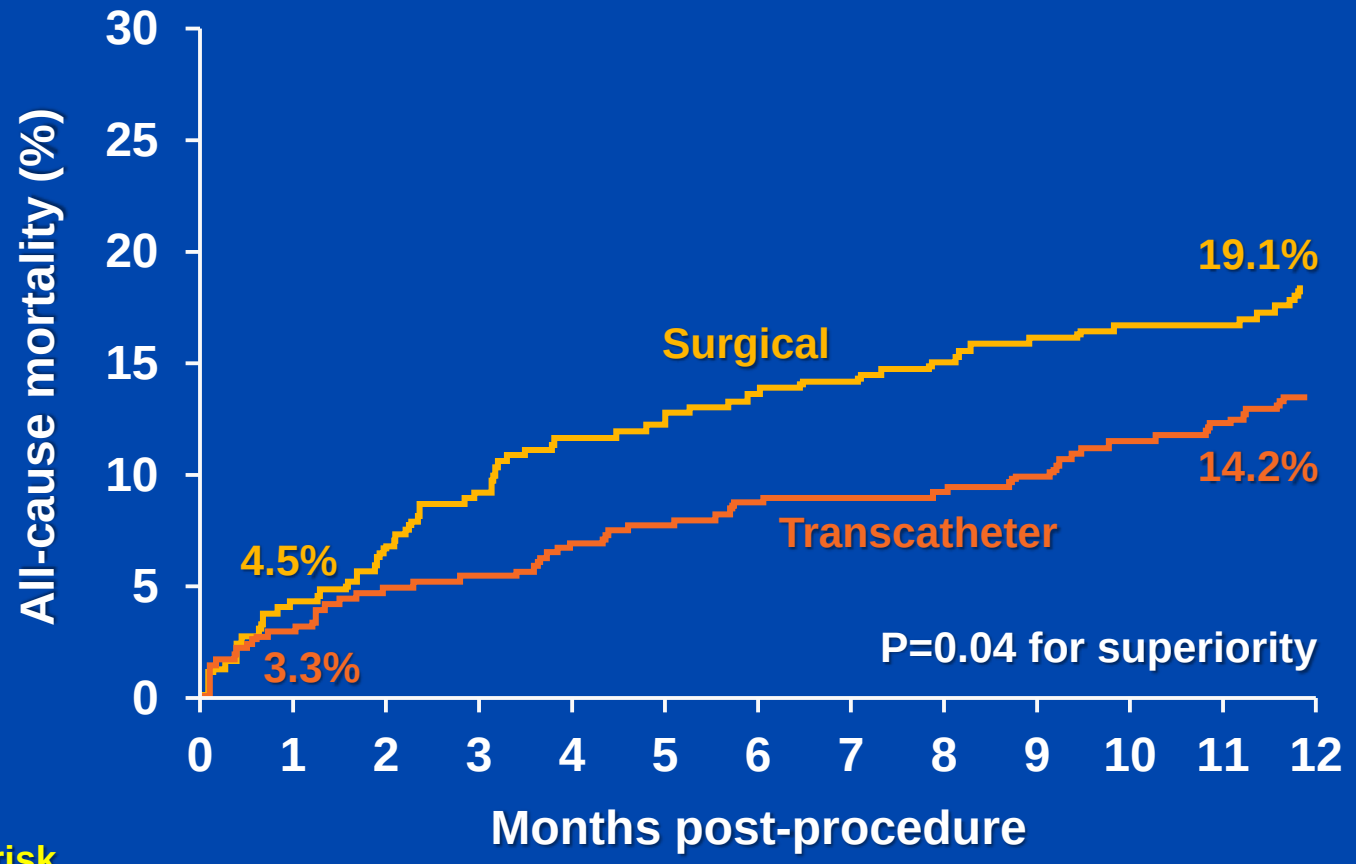
Primary Endpoint
1 Year All-Cause Mortality



No. at risk					
Surgical	357	341	297	274
Transcatheter	390	377	353	329

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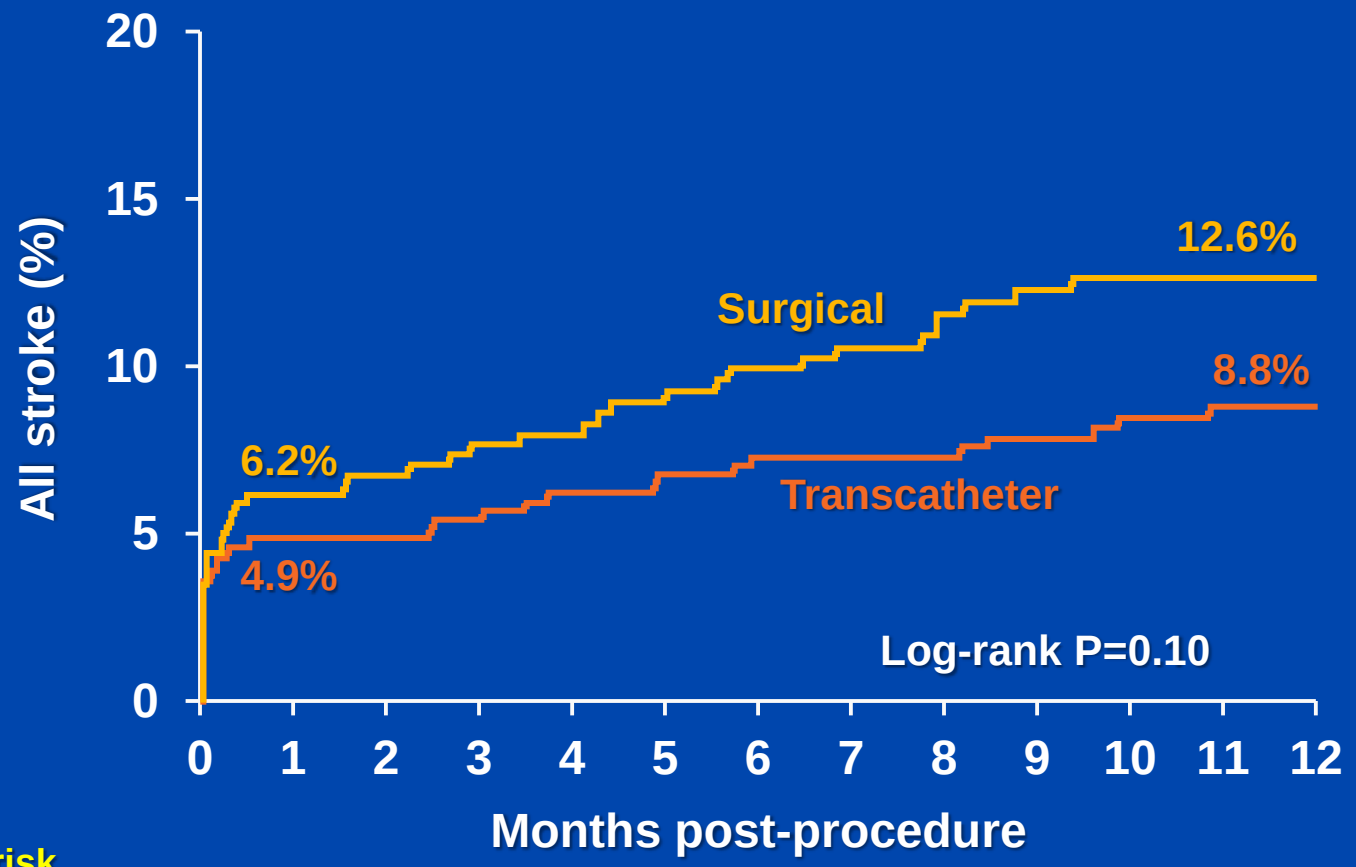
All Stroke



No. at risk					
Surgical	357	322	274		249
Transcatheter	390	363	334		314

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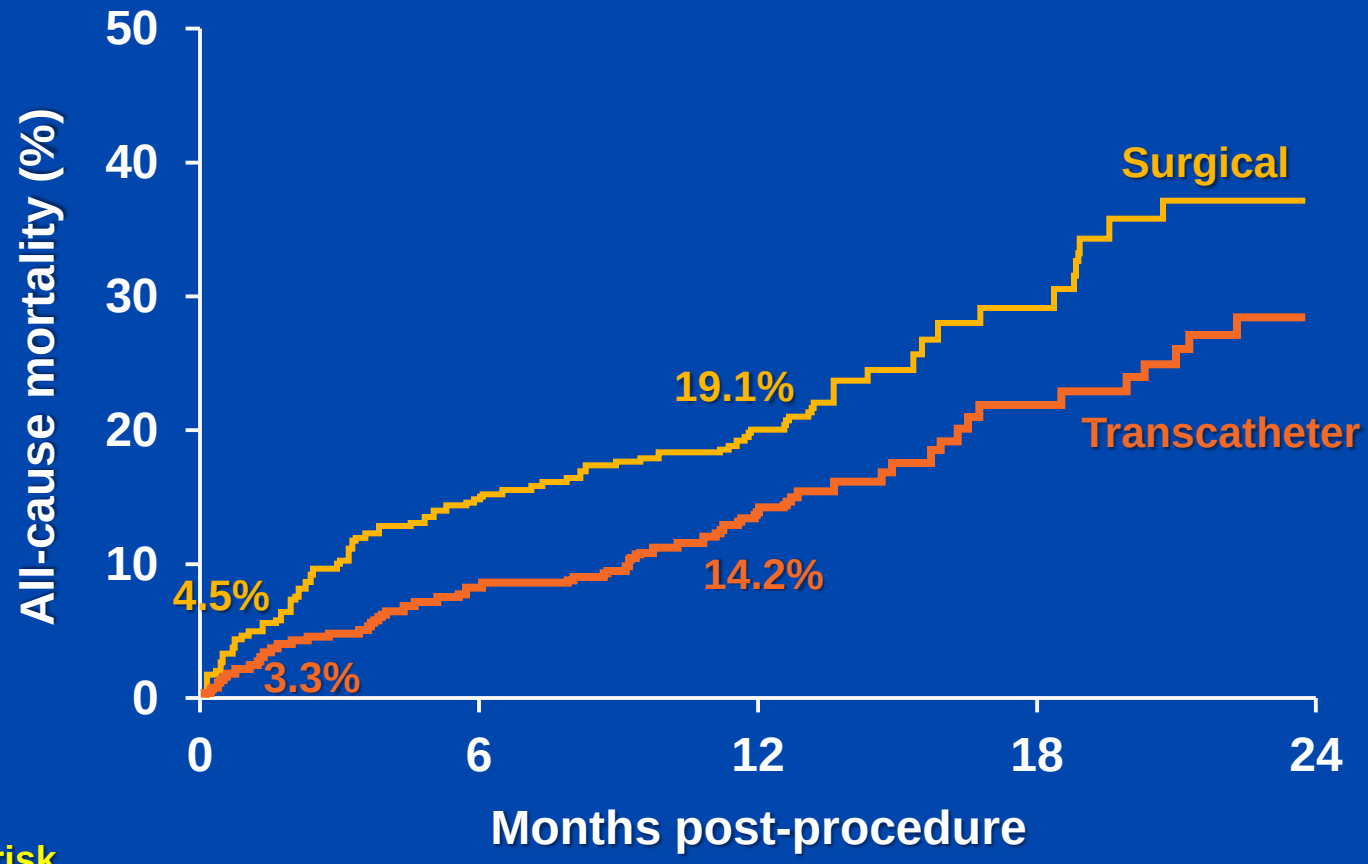
2-Year All-Cause Mortality



No. at risk				
Surgical	357	341	274	28
Transcatheter	390	377	329	38

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Conclusion

- We assessed the safety and effectiveness of TAVR with the CoreValve prosthesis compared to surgical valve replacement in symptomatic patients with severe aortic stenosis at increased surgical risk
- The rate of death from any cause at 1 year was significantly reduced with TAVR performed with the CoreValve prosthesis

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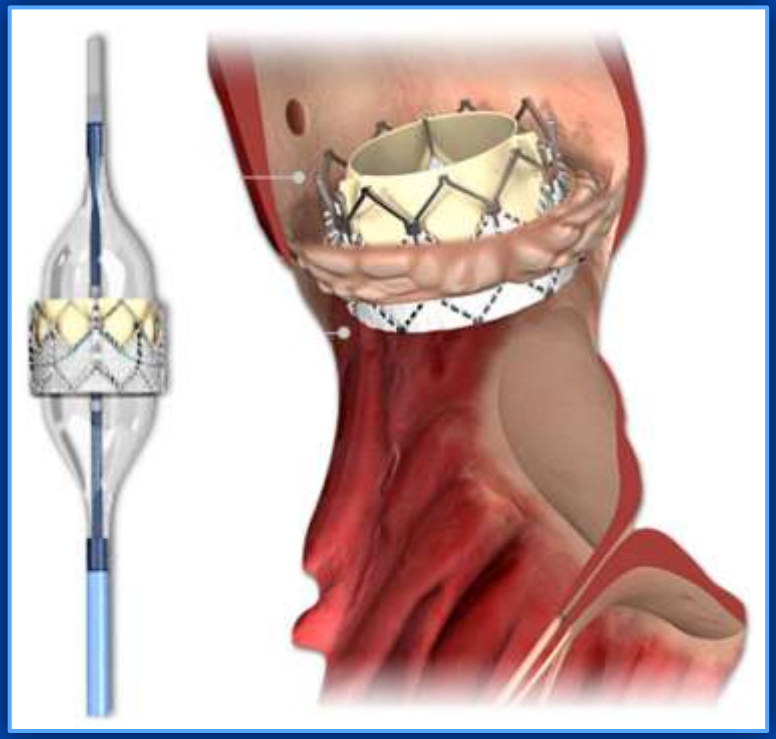
Background

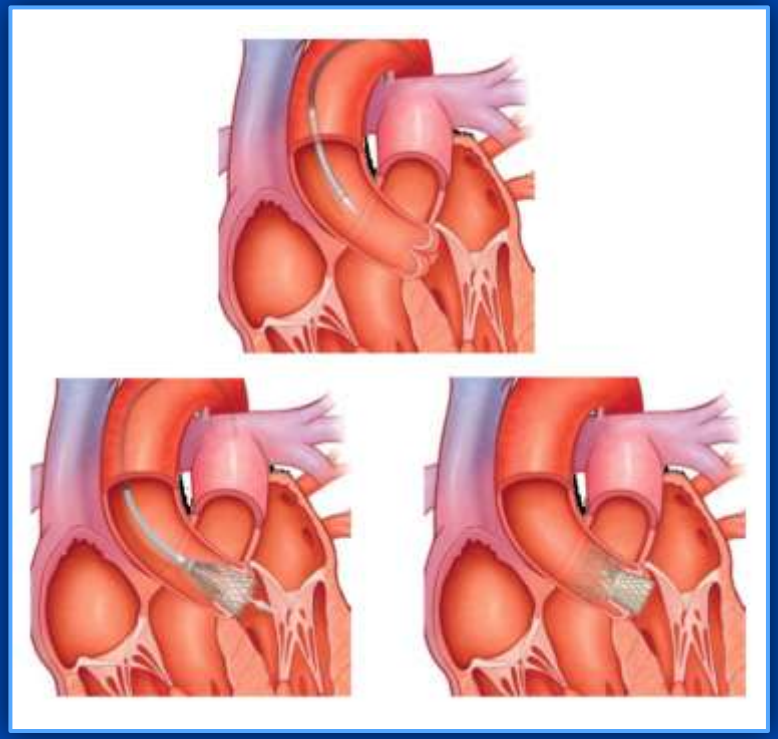
Balloon-expandable THV
Edwards Sapien XT

(Cobalt chromium stent frame, bovine pericardium)



Self-expandable THV
Medtronic CoreValue

(Nitinol stent frame, porcine pericardium)



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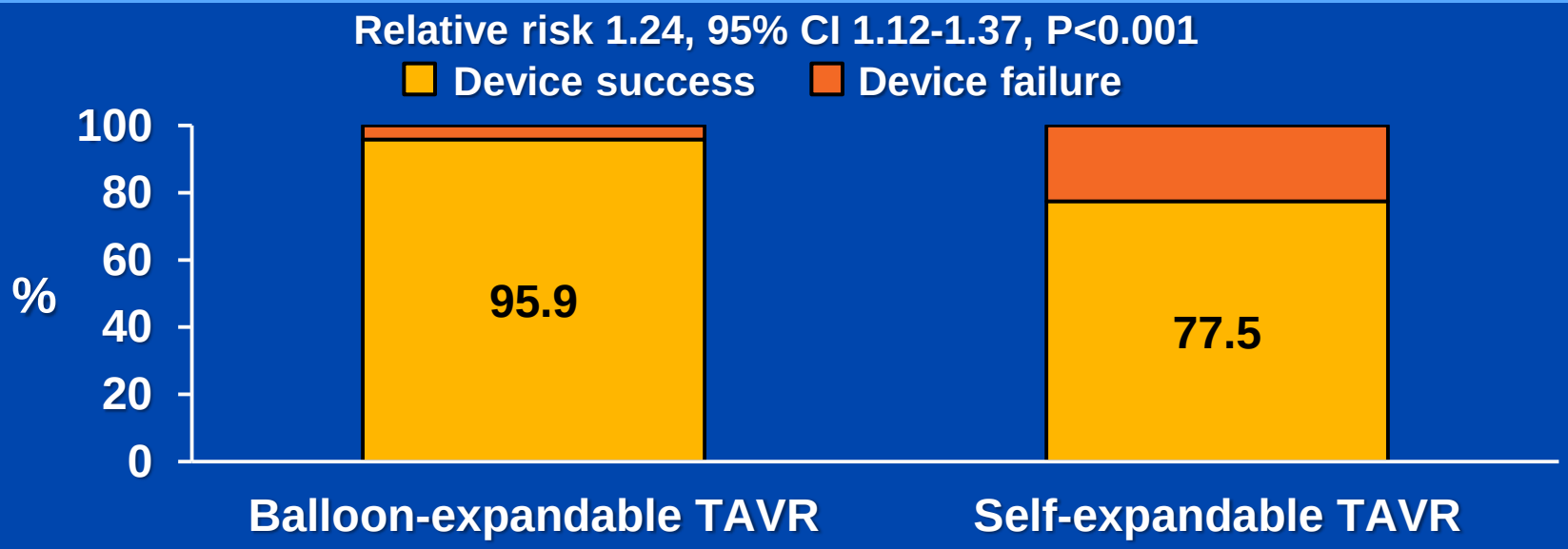
Primary Endpoint – Device Success



Causes of device failure	Balloon-expandable (n=121)	Self-expandable (n=120)
Unsuccessful vascular access, delivery and deployment	0/121 (0)	0/120 (0)
Incorrect position with implantation of >1 valve	1/121 (0.8)	7/120 (5.8)
Inadequate performance of the prosthetic heart valve		
Aortic valve area <1.2 cm^2 or mean aortic valve gradient >20 mm Hg	0/121 (0)	0/120 (0)
Moderate or severe prosthetic valve regurgitation	5/121 (4.1)	22/120 (18.3)
Total (hierarchical)	5/121 (4.1)	27/120 (22.5)

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Clinical Outcome at 30 Days

	Balloon-expandable (n=121)	Self-expandable (n=117)	P
Acute kidney injury	5/121 (4.1)	11/117 (9.4)	0.13
Repeat proc, for valve-related dysfunction	1/121 (0.8)	2/117 (1.7)	0.62
Combined safety endpoint	22/121 (18.2)	27/117 (23.1)	0.42
MACCE	8/121 (6.6)	4/117 (3.4)	0.38
Rehospitalization for HF	0/119 (0.0)	5/117 (4.3)	0.02
NYHA class improvement	100/106 (94.3)	91/105 (86.7)	0.06
Quality of life score	71.0±14.9	65.9±18.2	0.02
New permanent pacemaker	19/110 (17.3)	38/101 (37.6)	0.001

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There are no facts,
only interpretations.

-Friedrich Nietzsche

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Conclusions

- Among patients with high-risk aortic stenosis undergoing transfemoral TAVR, the use of a balloon-expandable valve resulted in a greater rate of device success than use of a self-expandable value
- At 30-days, improvement of heart failure symptoms was more frequently observed with the balloon-expandable valve, while minor stroke rates were numerically higher
- Long-term follow-up of the CHOICE population should be awaited, to determine whether the observed differences will translate into a clinically relevant overall benefit for the balloon-expandable valve

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Interpretations

- TAVR is used with increasing frequency in high risk and increasingly less high risk patients
- Hemodynamic improvement is excellent and sustained out to 5 years
- Clinical results are improving
  - Baseline co-morbid conditions are associated with adverse outcome
- A variety of devices are available and technology continues to iterate
- Risk prediction scores are being developed
- Goal:
  - Personalized medicine – match specific device for specific patient at right time

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TVT Registry Update

David R. Holmes, Jr., M.D.

Mayo Clinic, Rochester

Thursday AM Conference

April 2014

DISCLOSURE
Conference Director / Planning Committee

No Relevant Financial Relationship (s)

John Bresnahan, MD

Gurpreet Sandhu, MD

Jen Mears

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DISCLOSURE
David R. Holmes, Jr., M.D.

Relevant Financial Relationship(s)

None

Off Label Usage

None

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Learning Objectives

- What factor is associated with increased stroke at 1 year in patients undergoing TAVR?
- What is the relationship between increasing degrees of renal insufficiency and 1 year outcome of TAVR?
- What is the average number of days out of hospital at 6 months following TAVR in the TVT Registry?

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Valve in Valve Transcatheter Aortic Replacement for Degenerative Aortic Bioprosthesis: Initial Results from the STS/ACC TVT Registry

E. Murat Tuzcu, J. Matthew Brennan, Ralph Brindis, John Carroll, Fred Edwards, Frederick Grover, David Shahian, Eric Peterson, John Rumsfeld, David Holmes, Michael Mack

For TVT Registry

Conflict of Interest Disclosure

- No financial conflicts
- Member of Executive Committee of PARTNER Trial
- Principal investigator of SALUS Trial

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Background

- Bioprosthetic valves are used in >80% of AVR surgeries in US
- Durability of bioprosthesis is limited
- Valve-in-valve TAVR (ViV) is used in patients with failed surgical bioprosthesis who are at high risk for re-do AVR
- Data about ViV TAVR procedure is limited
- TVT registry includes data of most of the TAVR procedures in US (both for native valves and ViV procedures)

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Aim

To assess the in-hospital and one year outcomes of ViV TAVR in the TVT Registry

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Study Population

Procedural and in-hospital outcomes (250 sites)

- All patients undergoing TAVR entered into the TVT Registry November 2011-November 2013 from 250 sites

One-year outcomes (228 sites)

- All patients undergoing TAVR November 2011-July 31, 2013
- Age >65 years
- Medicare insurance
- Part A & B and non-HMO during month of index procedure
- Index admission linked to inpatient Medicare claims using direct patient identifiers (~97% successful record linkage rate)

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Methods

Safety and efficacy of ViV TAVR procedures using Edwards Sapien balloon expandable valve

- Comparison to TAVR for native valve AS
  - In-hospital
    - Procedural outcomes
    - Mortality
    - Stroke
  - One year
    - Mortality
    - Stroke
    - Days alive outside hospital

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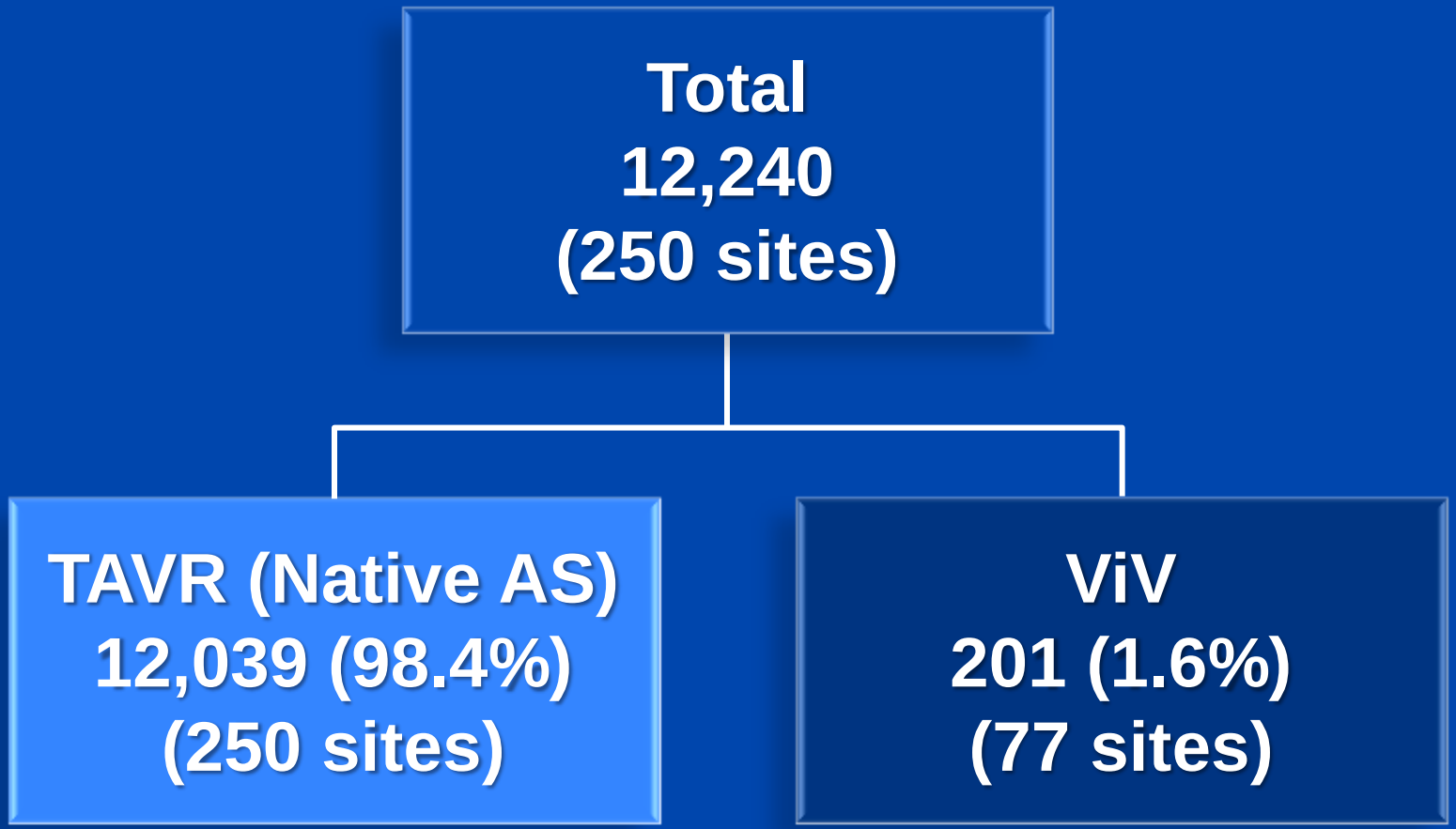
In-hospital Study Population



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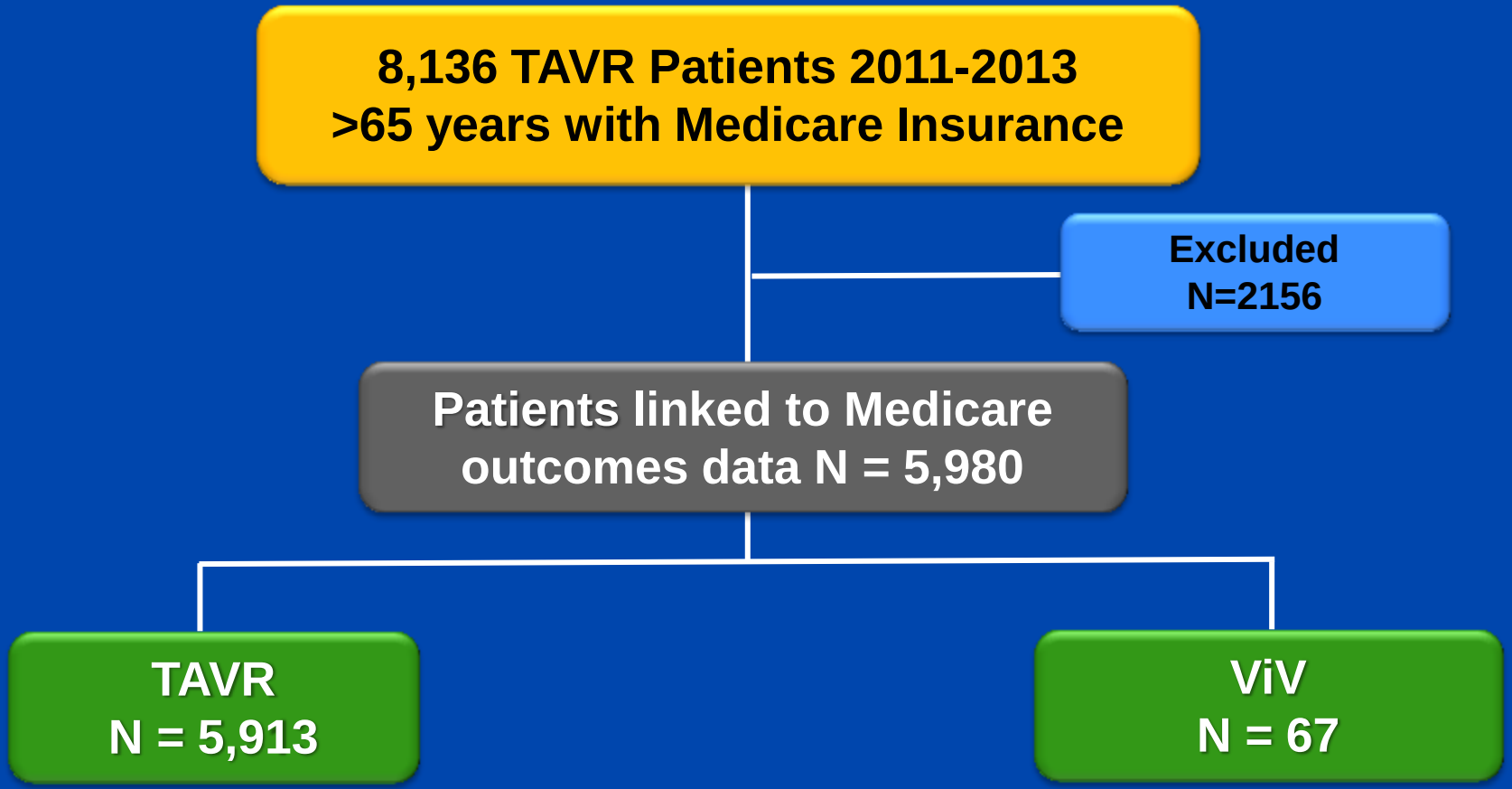
One Year Study Population



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Patient Characteristics (1)

Characteristic	TAVR (n=12,039)	ViV (n=201)	P
Age (yr)	84 (78-88)	77 (66-83)	<0.0001
Male sex (%)	48.9	60.5	0.001
STS Score	6.9 (4.6-10.6)	8.0 (4.7-11.0)	0.2
NYHA FC III, IV	83.0	91.8	<0.0001
Previous MI (%)	25.6	22.0	0.3
Prior CABG (%)	32.2	47.0	<0.0001
Prior PCI (%)	35.8	18.4	<0.0001

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Patient Characteristics (2)

Characteristic	TAVR (n=12,039)	ViV (n=201)	P
Peripheral vascular disease (%)	32.2	22.4	0.003
COPD			
Any	45.2	42.9	0.5
Oxygen dependent	14.3	11.1	0.2
On dialysis	4.2	8.0	0.01
Atrial fibrillation (%)	40.3	43.8	0.3
Permanent pacemaker (%)	16.9	22.4	0.04
Diabetes (%)	36.6	28.9	0.2
Hypertension (%)	88.8	85.1	0.09
Prior stroke	12.6	10.0	0.3
Porcelain aorta (%)	7.2	7.5	0.9
Hostile chest (%)	8.9	18.9	<0.0001

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Previous Valve Surgery

Events	TAVR (n=12,039)	ViV (n=201)	P
Previous cardiac surgery			
2	3.9	20.9	<0.0001
≥3	0.56	6.47	<0.0001
Mitral valve repair (%)	1.0	9.0	<0.0001
MVR (%)	1.6	8.0	<0.0001
Mechanical	1.0	1.5	
Bioprosthesis	0.6	6.5	

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Baseline Echocardiography

Echo findings	TAVR (n=12,039)	ViV (n=201)	P
AVA ($cm^{2)}$	0.64 (0.50-0.80)	0.71 (0.60-0.90)	<0.0001
AVG mean (mm Hg)	43.0 (36-53)	42 (29-54)	0.01
Mean LVEF (%)	57 (45-63)	55 (40-60)	0.0005
LVEF <30% (%)	7	13.7	0.0004
RVSP (mm Hg)	45 (36-56)	50 (39-64)	0.001
Moderate or severe MR (%)	36	47.4	0.0015
Moderate or severe TR (%)	32	47.6	<0.0001

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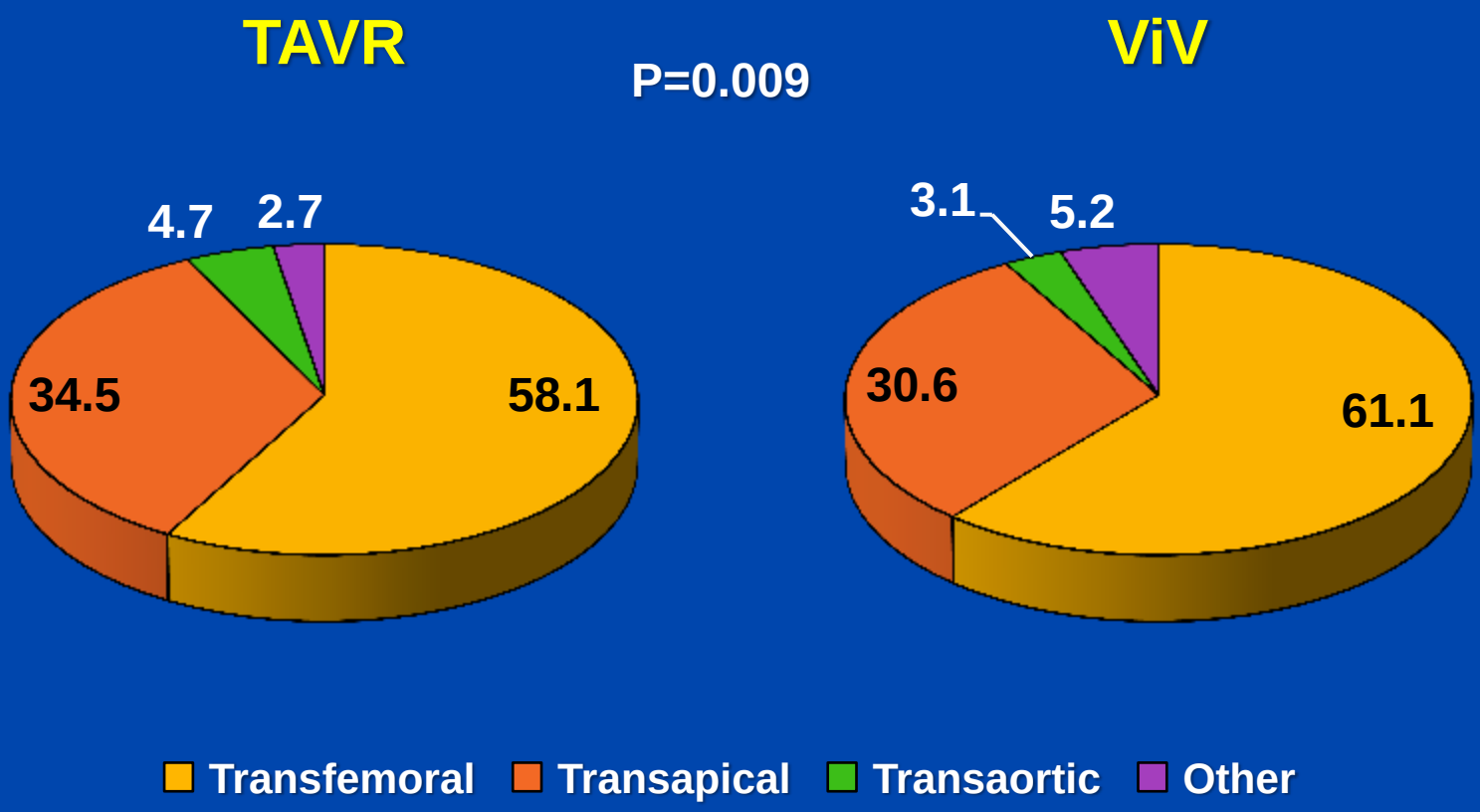
Access



Procedure

Events	TAVR (n=12,039)	ViV (n=201)	P
Fluoroscopy time (min)	17.3 (12.0-24.7)	19.7 (12.8-30.0)	0.009
Contrast volume (mL)	110 (73-170)	75 (35-128)	<0.0001
General anesthesia	98.1	98.0	0.9

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Procedural Complications (1)

Events	TAVR (n=12,039)	ViV (n=201)	P
Aborted procedure (%)	3.3	1.0	0.0743
Conversion to OHS (%)	1.3	1.4	0.8457
CP bypass (%)	4.2	3.5	0.6319
Use of 2nd valve (%)	2.4	1.0	0.2

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Procedural Complications (2)

Echo findings	TAVR (n=12,039)	ViV (n=201)	P
Coronary obstruction (%)	0.5	1.0	0.3
Device embolization (%)	0.7	0	0.4
Perforation (%)	1.1	0	0.1
Aortic dissection (%)	0.4	0	0.4
Device success (%)	92.2	88.4	0.0548

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Post-Procedure Echocardiography

Echo findings	TAVR (n=12,039)	ViV (n=201)	P
AVA (cm^2)	1.6 (1.3-2.0)	1.3 (1.0-1.5)	<0.0001
AVG mean (mm Hg)	10 (7-13)	18.5 (12-26)	<0.0001
Moderate or severe PV-AR (%)	9.5	2.8	0.05
Moderate or severe MR (%)	13.1	20.4	0.6072

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In-Hospital Events

Events	TAVR (n=12,039)	ViV (n=201)	P
VARC major bleeding (%)	3.3	3.6	0.8
Vasc comp requiring Rx	5.7	5.0	0.7
AFib (%)	6.9	3.5	0.06
New pacemaker (%)	6.8	3.5	0.06
ICU stay (hrs)	46 (25-78.5)	48 (25.3-74.7)	0.6
LOS (days)	6 (4-10)	8 (5-16)	<0.0001
Discharge to home (%)	58.2	71.1	0.0003

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In-Hospital Death and Stroke

Events	TAVR (n=12,039)	ViV (n=201)	P
Death (all cause) (%)	5.4	4.0	0.4048
Stroke (%)	2.1	2.5	0.6661

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Access and Outcome of ViV-TAVR

Events	Femoral (n=123)	Non-femoral (n=78)	P
STS (%)	7.8 (4.6,10.4)	8.8 (5.0,12.6)	0.1
Death (%)	2.5	6.6	0.2
Stroke (%)	3.3	1.3	0.4

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In-Hospital Outcome – Mode of Prosthesis Failure

Events	AS (n=118)	AR (n=35)	AS+AR (n=32)	P
STS (%)	7.9 (4.7,10.9)	6.5 (4.7,10.4)	8.8 (4.9,10.8)	0.9
Death (%)	4.2	2.9	6.3	0.8
Stroke (%)	3.4	0.0	3.1	0.6
AVG_m (mm Hg)	19.5 (13,27)	14.5 (10,20)	24 (15,30)	0.009

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In-Hospital Outcome – Size of the ViV Device

Events	23 mm valve (n=134)	26 mm valve (n=58)	P
Death (%)	5.3	1.8	0.3
Stroke (%)	3.0	1.7	0.6
AVG_m (mm Hg)	21 (14.5,27.5)	14 (10,20)	0.0002

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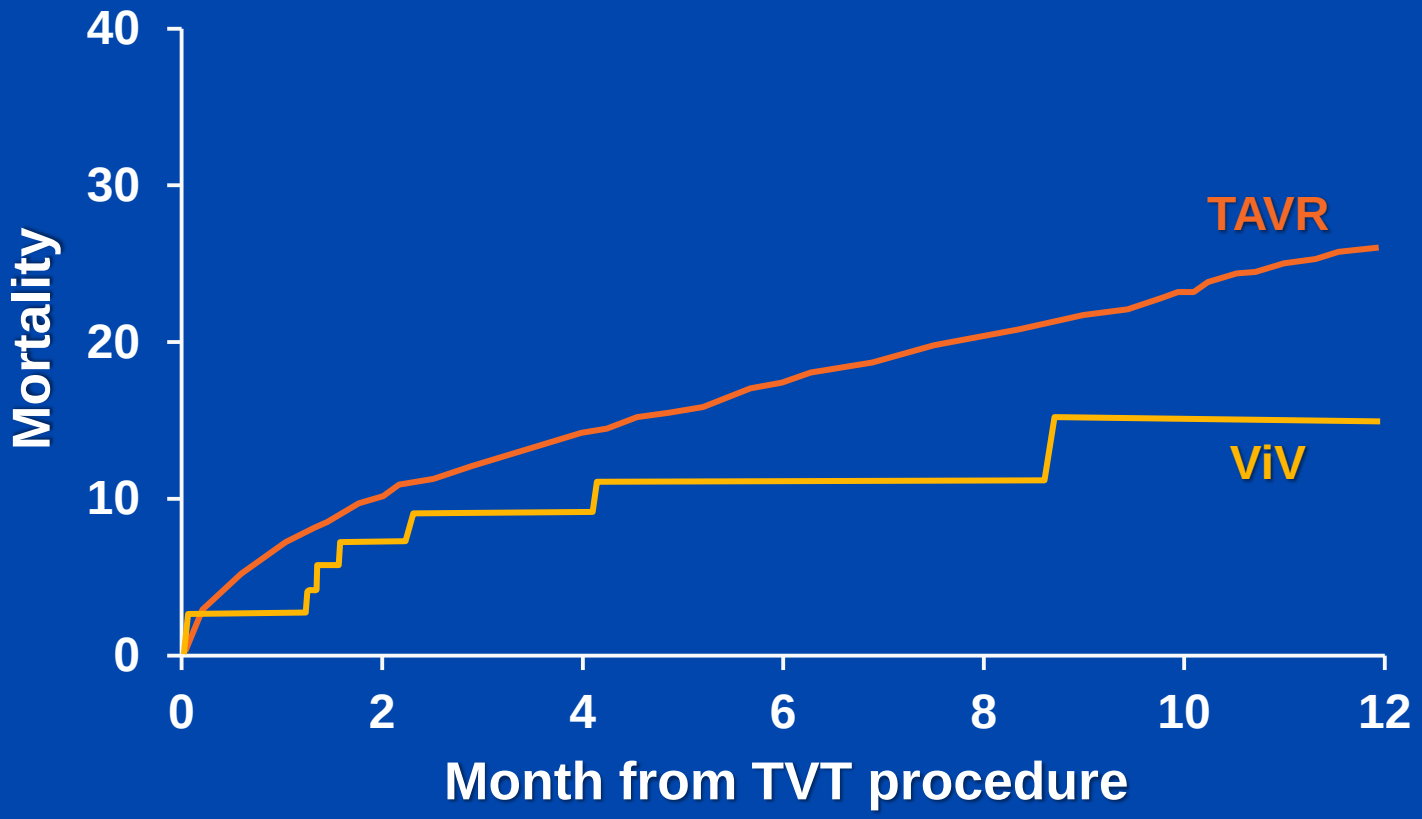
Mortality



Mortality	ViV (n=67)	TAVR (n=5913)	P
30 day (%, 95% CI)	3 (0.6-9.3)	7.3 (6.7-8.0)	0.130
6 month (%, 95% CI)	11.5 (5.0-21.2)	17.8 (16.8-18.9)	
1 year (%, 95% CI)	15.4 (6.5-27.8)	26.4 (24.8-27.9)	

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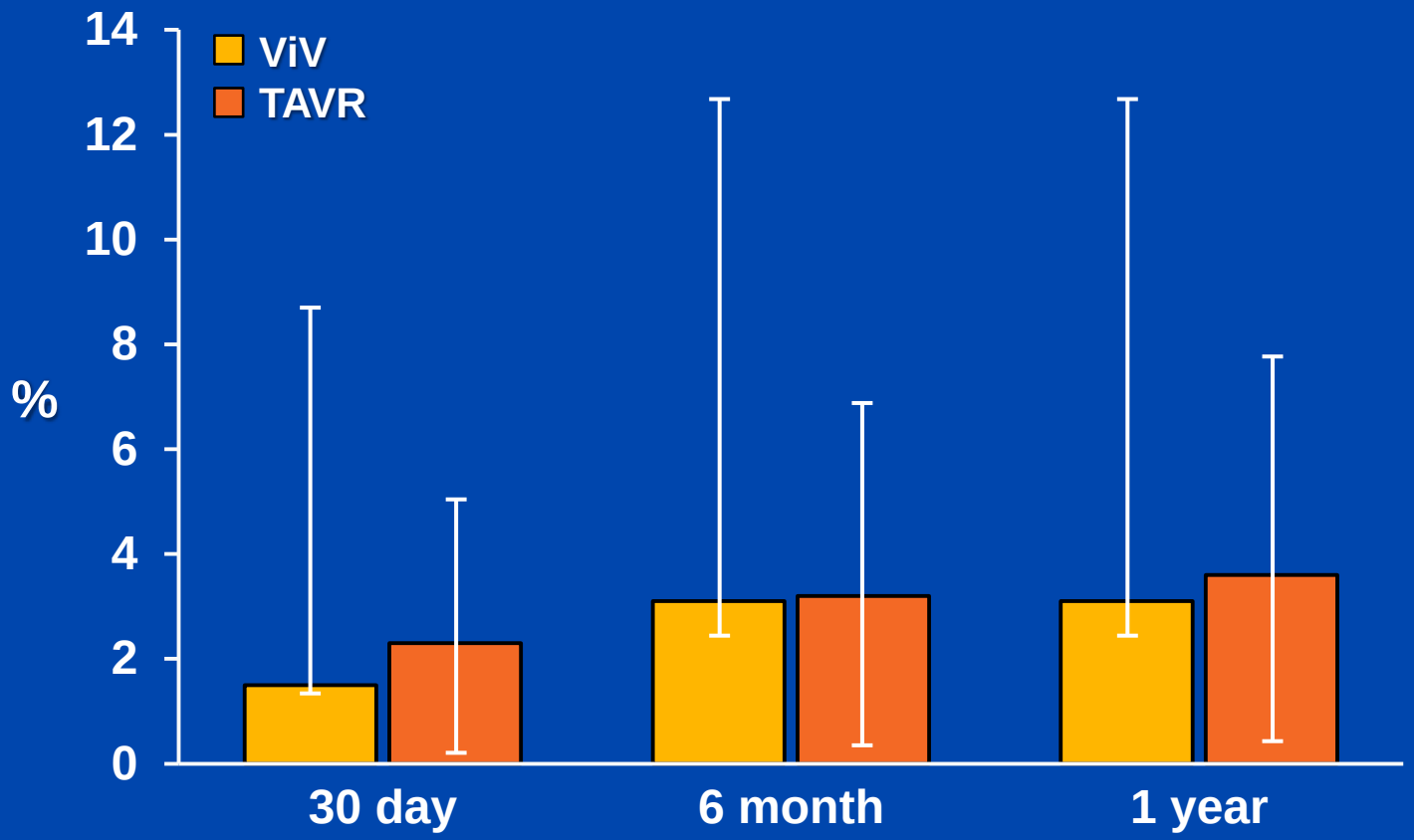
Stroke



Mortality	ViV (n=67)	TAVR (n=5913)	P
30 day (%, 95% CI)	1.5 (0.1-7.2)	2.3 (2.0-2.8)	0.893
6 month (%, 95% CI)	3.1 (0.6-9.6)	3.2 (2.8-3.7)	
1 year (%, 95% CI)	3.1 (0.6-9.6)	3.6 (3.1-4.2)	

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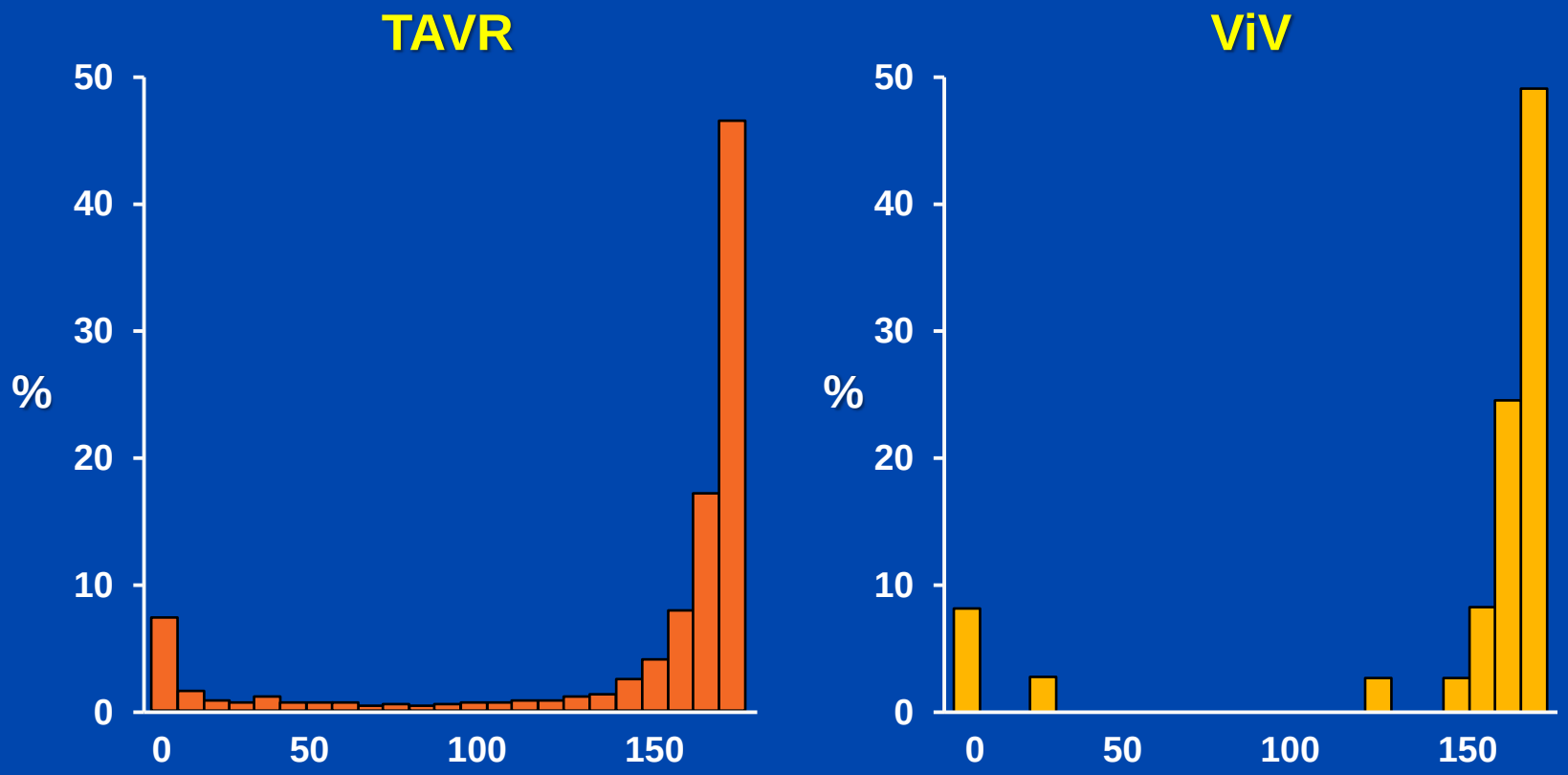
Number of Days Alive and Out of the Hospital



	ViV	TAVR	P
Median (days)	172 (164,177)	171 (152,175)	0.184

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Limitations

- Data about the failed bioprosthesis type and size are unavailable
- Not all patients could be linked to CMS data
- 30 days and 1 year follow-up is not complete
- Quality of life analysis is not finalized

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Conclusion

- Valve in valve procedure with the approved Sapien valve is safe and feasible
  - Mortality : 4.0%
  - Stroke: 2.5%
- Device success is achieved in a high percentage of cases
- Valve in valve TAVR results in hemodynamic improvement although aortic valve area is less than seen after TAVR for native valves
- One year outcomes although limited suggest continued safety and efficacy

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Ongoing Analysis

- Investigation of the hemodynamic and clinical outcomes in relation to
  - Bioprosthesis type and size
  - Patient characteristics
- Additional data on functional improvement and long term outcomes are being collected

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Conclusion (1)

- Of all TAVR procedures 1.6% is performed for the treatment of failed surgically placed prosthesis
- ViV patients have a similar device success and procedural complication rates as other TAVR patients
- In-hospital adverse events are similar in ViV and other TAVR patients; but after ViV hospital stay in longer
- In-hospital mortality and stroke in ViV patients are 4.0% and 2.5% respectively, similar to other TAVR patients
- Post-procedure valve gradient is higher and effective orifice area smaller in ViV patients than other TAVR pts
- Moderate or severe paravalvular aortic regurgitation is significantly less common after ViV TAVR

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Conclusion (1) – Dave Shahian Edits

- 1.6% of TAVR procedures performed to treat failed surgically placed prosthesis
- Compared with other TAVR patients, ViV patients
  - Similar device success and procedural complication rates
  - Similar in-hospital adverse events
  - Longer LOS
  - Similar in-hospital mortality (4%) and stroke (2.5%)
  - Higher post-procedure valve gradient
  - Smaller EOA smaller
  - Less commonly have moderate or severe paravalvular aortic regurgitation
  - Discharged home more frequently
  - Similar number of days alive and out of the hospital

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Conclusion (2)

- ViV patients are discharged home more frequently than other TAVR patients
- Patients undergoing TAVR by a non-TF approach have comparable outcomes after ViV TAVR
- Patients who received a 23 mm valve have similar in hospital death and stroke rates, but their valve gradient is higher
- One-year mortality and stroke rates of ViV patients are similar to those who underwent TAVR for native valve stenosis
- Patents in the ViV and other TAVR groups have similar number of days alive and out of the hospital
- Transcatheter valve replacement inside a previously placed surgical bioprosthesis appears to be safe and feasible
- Further study of larger patient populations is needed for long term outcome and functional improvement

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Conclusion (2) – Dave Shahian Edits

- Non-TF TAVR and non-TF ViV have comparable outcomes
- 23 mm and 26 mm ViV recipients have similar in hospital death and stroke rates, but 23 mm valve gradient higher
- One-year mortality and stroke rates of ViV patients comparable to those for native valve stenosis TAVR
- Transcatheter valve replacement inside previously placed surgical bioprosthesis appears safe and feasible
- Further study of larger patient populations needed for long-term outcomes and functional improvement

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Outcomes of Transcatheter Aortic Valve Replacement in Patients with End-Stage Renal Disease

A Report from the STS/ACC TVT Registry

Michael Mack, J. Matthew Brennan, Sarah Milford-Beland, Dadi Dai, Ralph Brindis, John Carroll, Fred Edwards, Fred Grover, Sean O'Brien, Eric Peterson, John Rumsfeld, Dave Shahian, Vinod Thourani, E. Murat Tuczu, Alan Zajarias, David Homes
For the TVT Registry

Conflict of Interest Disclosure

- Executive committee member of the PARTNER Trial of Edwards Lifesciences

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Background

- Aortic stenosis (AS) is the most common valvular lesion in patients with end-stage renal disease (ESRD)
- 30-day mortality in dialysis patients with AS undergoing surgical aortic valve replacement (SAVR) ranges from 13.8*-17.3%†
- 1-year mortality after SAVR in elderly dialysis patients is 34-53%**
- Outcomes of transcatheter aortic valve replacement (TAVR) in patients on dialysis are not known since they were excluded from the pivotal trials
- Assessed early and 1-year outcomes of TAVR in dialysis patients captured in the TVT registry

*Thourani: Ann Thorac Surg 91:1798, 2011; †Horst: Ann Thorac Surg 69:96, 2000;
**Brennan et al: Circ 127:1647, 2013

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Study Population

- Procedural and in-hospital outcomes (250 sites)
  - All pt undergoing TAVR entered into the TVT registry November 2011-November 2013 from 250 sites
- 1-year outcomes (228 sites)
  - All pt undergoing TAVR November 2011-July 31, 2013
  - Age >65 years
  - Medicare insurance
  - Part A & B and non-HMO during month of index procedure
  - Index admission linked to in-patient Medicare claims using direct pt identifiers (~97% successful record linkage rate)

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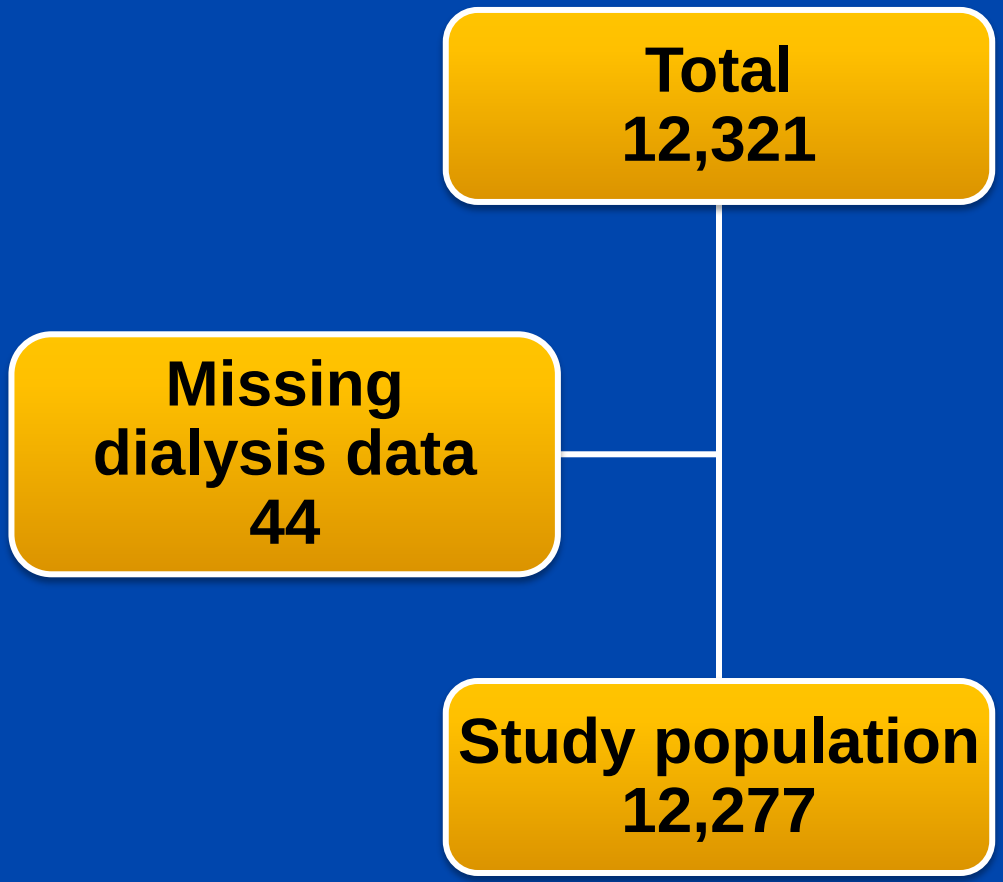
TAVR in TVT Registry
November 2011-2013



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Patient Characteristics

	No dialysis n=11,749	Dialysis n=528	P
Age	84	77	<0.0001
Median (IQR)	(78, 88)	(69, 84)	
Male gender (%)	48.5	58.3	<0.0001
Black/African American race (%)	3.3	11.4	<0.0001
STS PROM (%)	6.76	14.43	<0.0001
Median (IQR)	(4.51, 10.23)	(9.50, 20.07)	

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Patient Characteristics

	No dialysis n=11,749	Dialysis n=528	P
Hypertension (%)	88.6	92.8	0.0028
Diabetes (%)	35.7	54.4	<0.0001
PAD (%)	31.5	40.3	<0.0001
Prior MI	25.2	30.5	0.0063
NYHA class III-IV	80.7	87.5	<0.0001

No differences in
Prior PCI/CABG
Prior stroke
COPD
Atrial fibrillation

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Baseline Studies

	No dialysis n=11,749	Dialysis n=528	P
Hemoglobin (g/dL)	11.7 (10.5, 12.9)	10.5 (965, 11.5)	<0.0001
Serum albumin (g/dL)	3.7 (3.3, 4.0)	3.4 (3.0, 3.8)	<0.0001
FEV 1 (% predicted)	71 (55, 88)	61 (48, 76)	<0.0001
% LVEF <45%	21	30.5	<0.0001
Mod-severe MR (%)	35.8	42.1	0.0059
Mod-severe TR (%)	31.6	41.6	<0.0001

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Procedural Approach and Outcomes

	No dialysis n=11,749	Dialysis n=528	P
Transfemoral (TF) approach (%)	57.2	55.9	0.793
Device success (%)	89.3	86.6	0.157
Second valve (%)	4.3	6.4	0.01
Access complications	5.6	7.8	0.02

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Transfemoral vs Other Access

	TF n=295	Other access n=218	P
Female (%)	37.6	46.8	0.03
Prior CABG (%)	74.6	63.8	0.008
EuroSCORE II (%)	6.5 (4, 11)	8.9 (5, 11)	0.002
STS PROM (%)	12.9 (9, 18)	17.2 (11, 23)	<0.0001
O:E ratio	7.5/14.9 (0.50)	11/18.4 (0.59)	
Stroke (%)	2	0.5	0.13
VARC major bleed (%)	8.3	3.8	0.045
LOS (IQR) (days)	6 (4, 12)	9 (7, 15)	<0.0001

O:E calculated from STS PROM mean

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Mortality vs Predicted Risk

	STS <8 n=89	STS 8-15% n=190	STS >15 n=248	P
STS PROM (%)	6.3 (4.8, 7.2)	11.3 (9.6, 13)	20.5 (17.6, 26.8)	<0.0001
In-hospital mortality (%)	5.6	7.4	11.3	0.19

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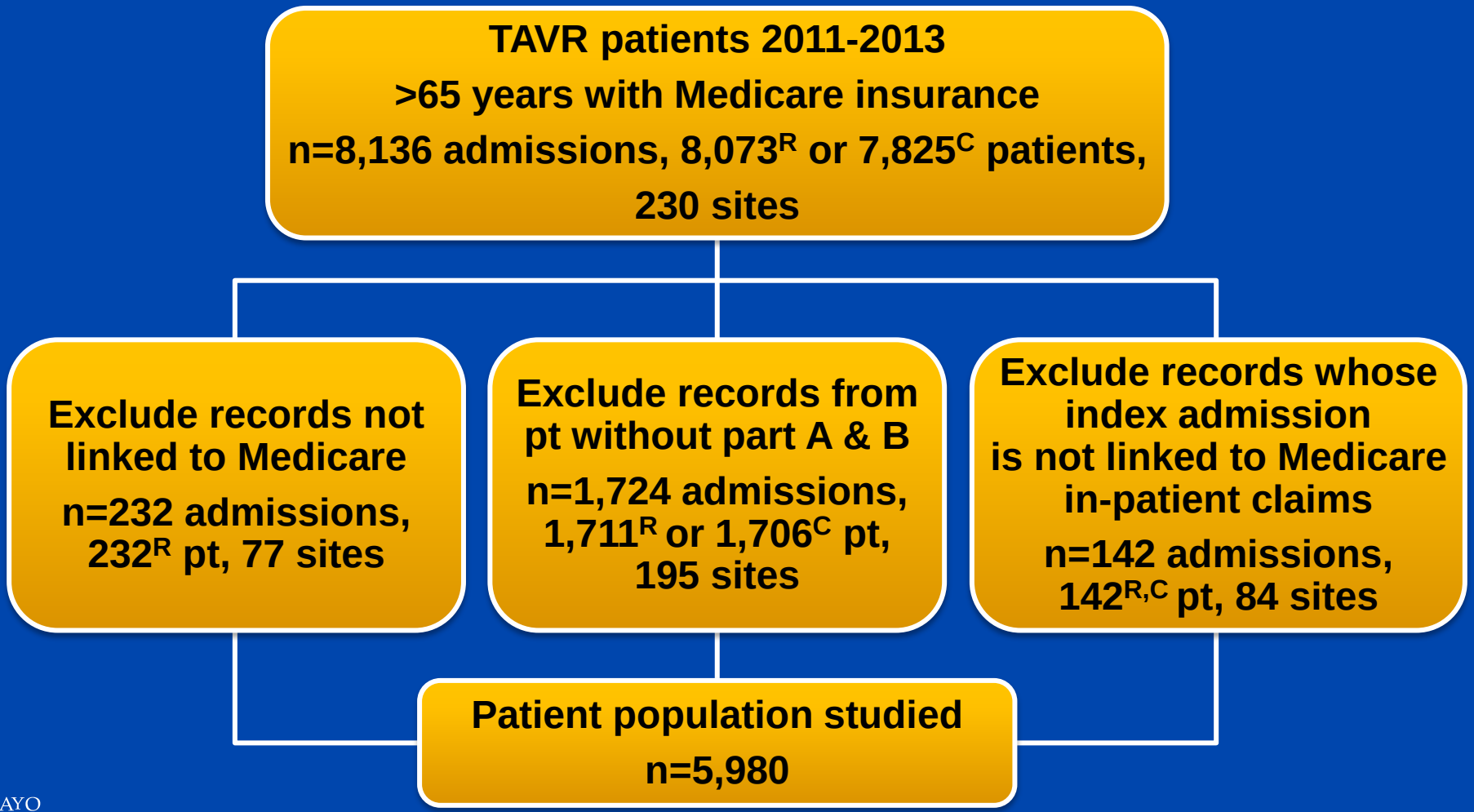
1 Year Study Population



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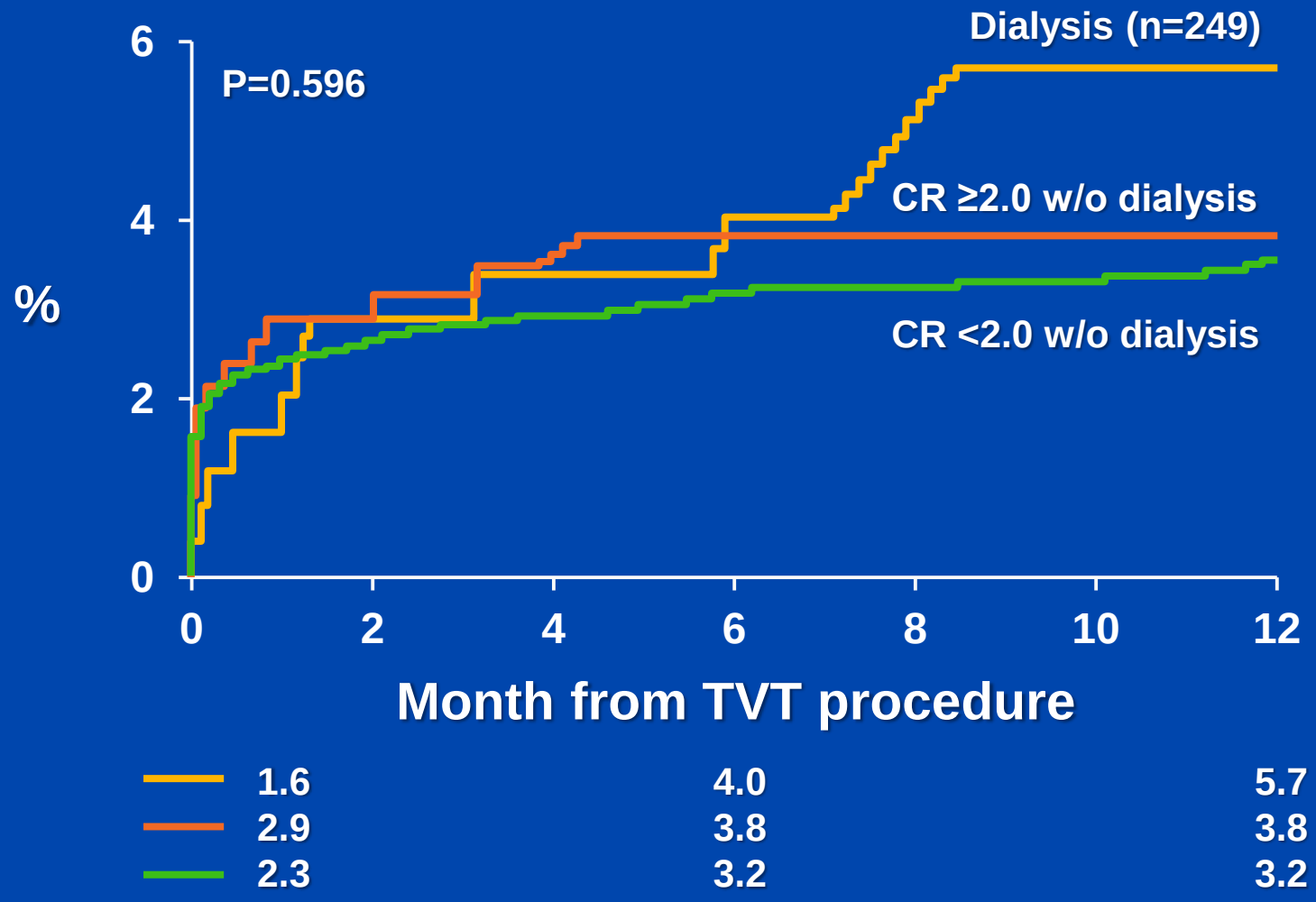
Stroke



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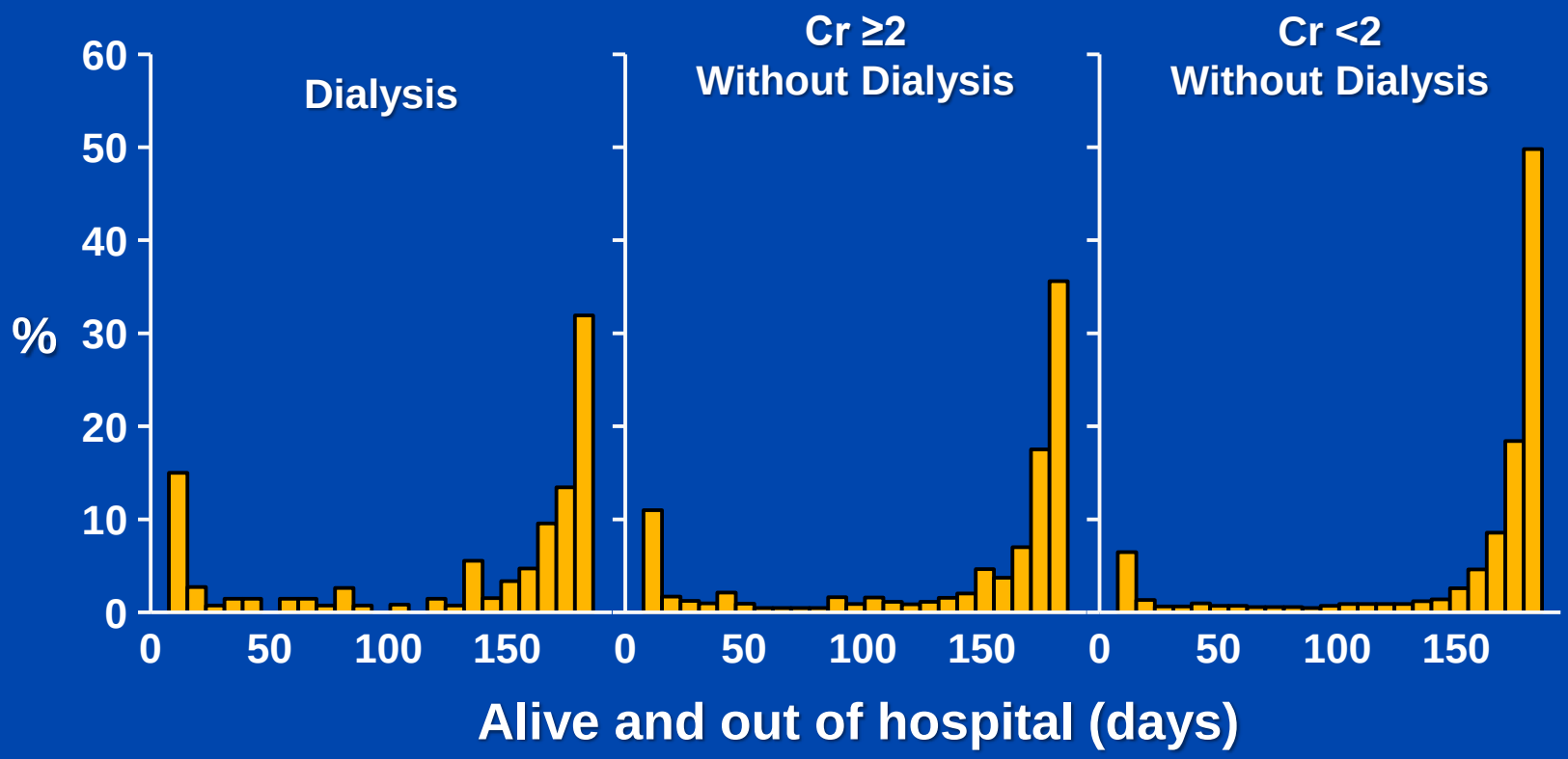
Days Alive and Out of Hospital

Renal Function



	Dialysis	Cr ≥2	CR <2	P
Median (days)	160	165	171	<0.001

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Summary

- Dialysis patients undergoing TAVR are younger, more commonly male and African American with significantly higher STS PROM
- Dialysis patients have a higher incidence of hypertension, PAD, CHF and diabetes
- In-hospital mortality and stroke in dialysis patients are 8.9% and 1.3% respectively
- In-hospital outcomes are worse in ESRD patients but are related to the higher comorbidities as reflected by the STS PROM

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Summary (cont)

- Patients undergoing TAVR by a non-TF approach are at significantly higher risk but have comparable outcomes
- Almost half the patients with ESRD are very high risk (STS >15) and have in-hospital mortality of 11%
- ESRD is an independent predictor of mortality at 1 year
- 1-year mortality is 46% in dialysis patients compared with 24% in patients with Cr <2.0

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Conclusions

- The TVT registry has comprehensive data on the early clinical outcomes of a subgroup of patients not studied in randomized clinical trials
- Linkage with CMS administrative claims data enabled assessment of outcomes at 1 year post- procedure
- Outcomes at 30 days and 1 year in patients with ESRD are significantly worse than in patients without renal disease
- TAVR outcomes are comparable to but not any better than historical outcomes of surgical AVR
- Functional, quality of life and longer term outcomes assessment is necessary
- Based on this data, the heart team should closely evaluate the candidacy of dialysis patients for TAVR especially those with significant comorbidities and STS PROM >15%

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One Year Outcomes from the STS/ACC Transcatheter Valve Therapy (TVT) Registry

David R. Holmes, Jr., J. Matthew Brennan, John S. Rumsfeld, David Dai, Fred Edwards, John Carroll, David Shahian, Fred Grover, E. Murat Tuzcu, Eric Peterson, Ralph Brindis, Michael J. Mack

March 2014
On behalf of the TVT Registry
ACC 2014
Washington, D.C.

Background

- TAVR is being used with increasing frequency
- Prior TVT Registry data on a subset of patients reported in-hospital and 30-day outcomes in U.S. clinical practice (Mack, et al JAMA 2013)
- Although longer-term outcomes have been reported in clinical trials, such outcomes in routine clinical practice in the U.S. are unknown
- The National STS/ACC TVT Registry was developed to capture the denominator of all U.S. patients undergoing TAVR

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Primary Outcomes

- This late breaking clinical trial presents the first TAVR data in the National TVT Registry linking initial outcome and 1-year Administrative Claims Center for Medicare Statistics (CMS). Patients undergoing TAVR for native aortic stenosis with an approved device were evaluated.
- Primary outcomes:
  - All cause mortality
  - Composite
    - Mortality and days alive outside of hospital
  - Stroke

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Patient Characteristics

Characteristic	Study Cohort N = 5,980
Prev. Stroke, n (%)	764 (12.8)
Peripheral Arterial Disease, n (%)	1,856 (31.1)
COPD Severe, n (%)	801 (13.5)
Oxygen-dependent lung disease, n (%)	895 (15.2)
Dialysis dependent	249 (4.2)
Serum creatinine <2.0	5,286 (88.8)
5mm walk time >6 sec	1,796 (30.4)
LV EF	
<30%, n (%)	414 (7.2)
>45%	4,276 (74.0)
Pre-TAVR Moderate MR, n (%)	1,594 (31.2)

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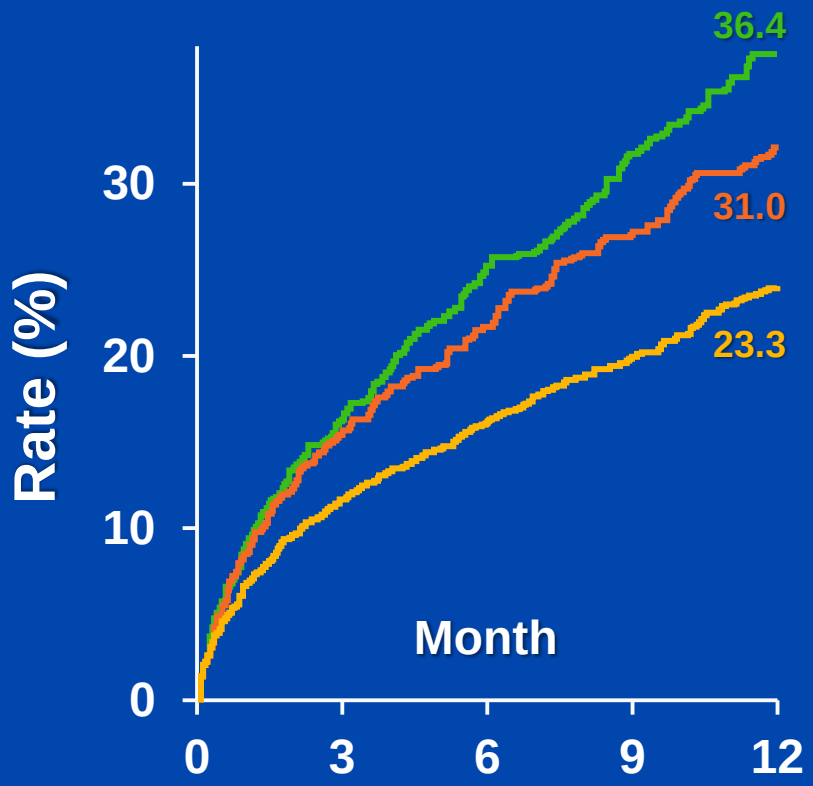
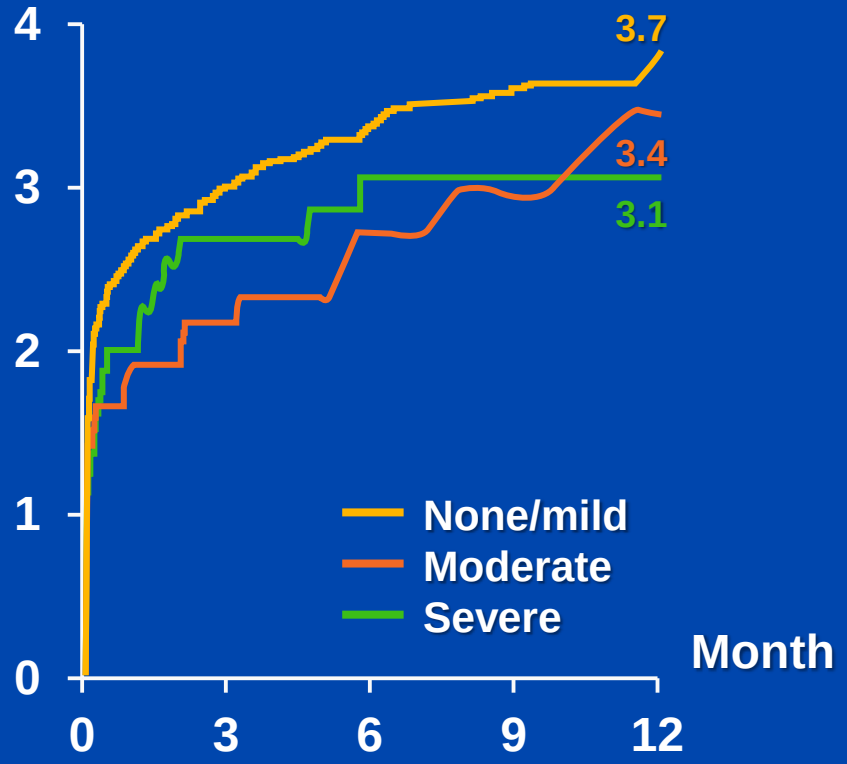
Cumulative Incidence of Death and Stroke
Affect of COPD

Mortality



	HR	P
Moderate vs None/mild	1.157	0.090
Severe vs None/mild	1.407	<0.001

Stroke



	HR	P
Moderate vs None/mild	0.793	0.363
Severe vs None/mild	0.937	0.806

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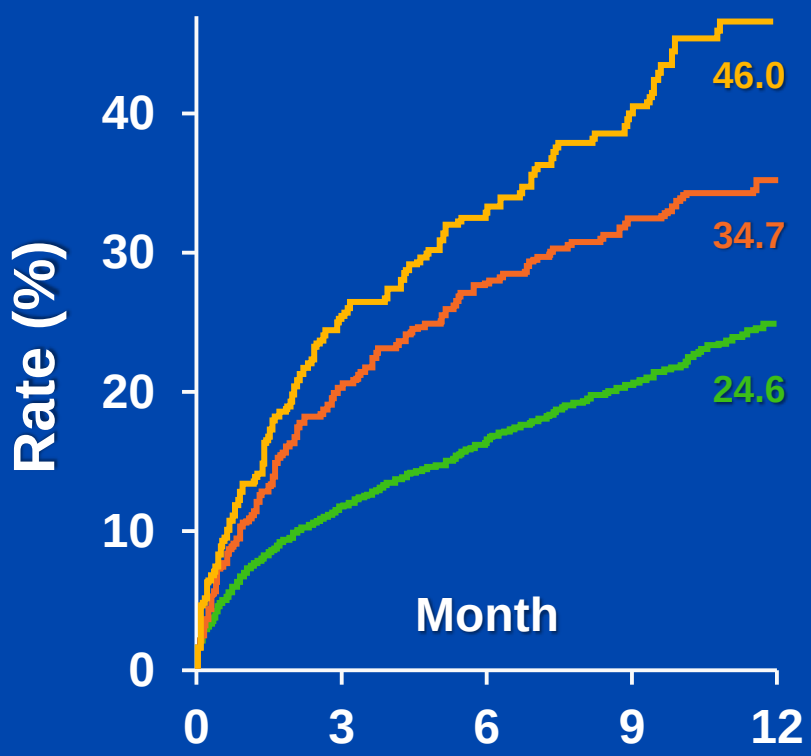
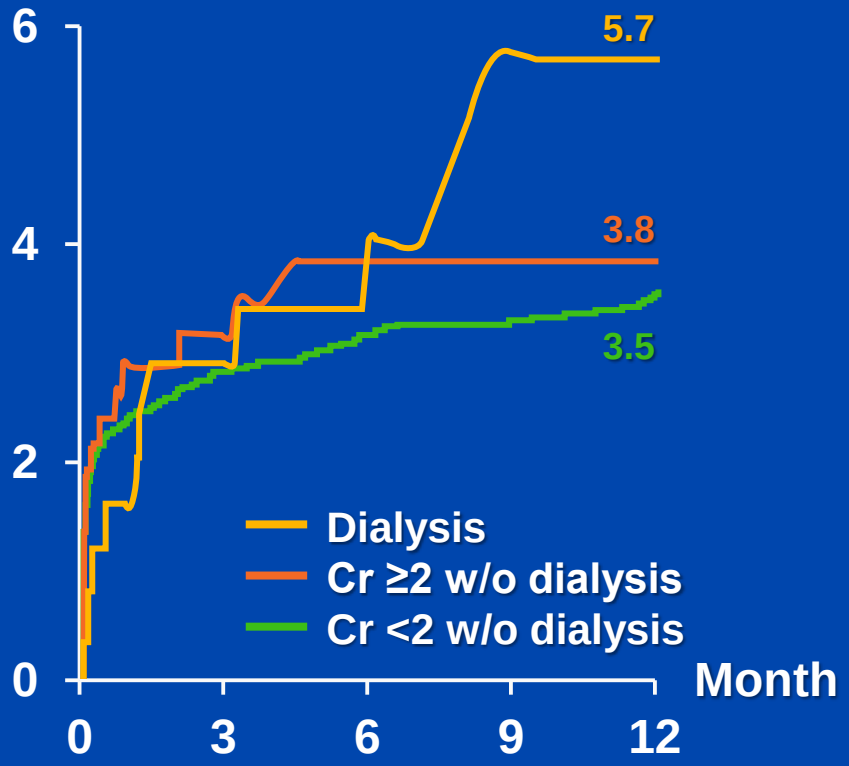
Cumulative Incidence of Death and Stroke
Affect of Renal Function

Mortality



	HR	P
Cr≥2 w/o dialysis vs Cr<2 w/o dialysis	1.348	0.005
Dialysis vs Cr<2 w/o dialysis	1.805	<0.001

Stroke



	HR	P
Cr≥2 w/o dialysis vs Cr<2 w/o dialysis	1.244	0.479
Dialysis vs Cr<2 w/o dialysis	1.244	0.578

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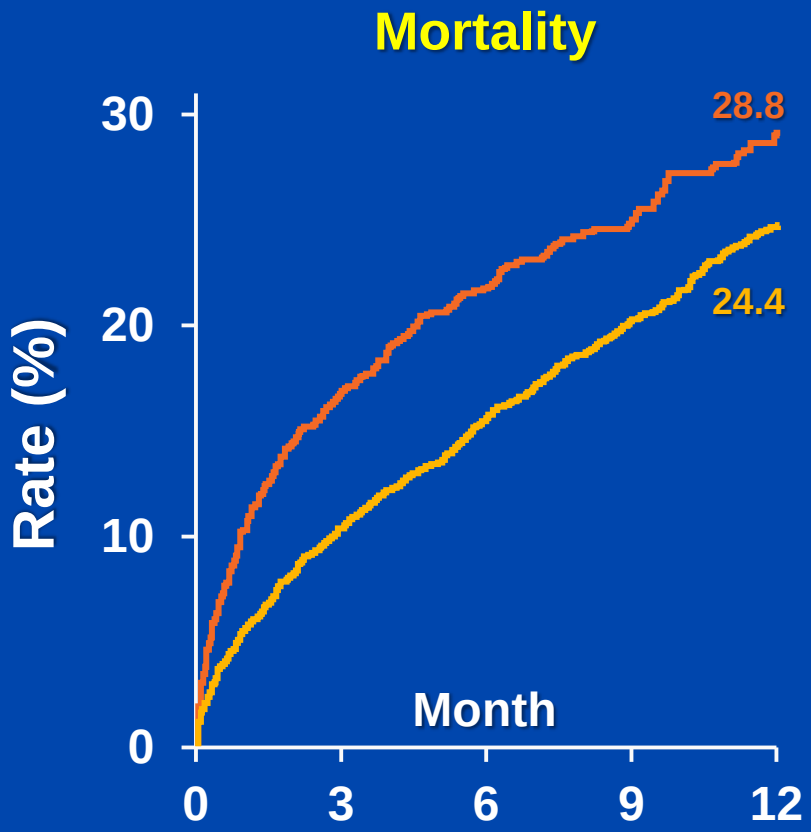
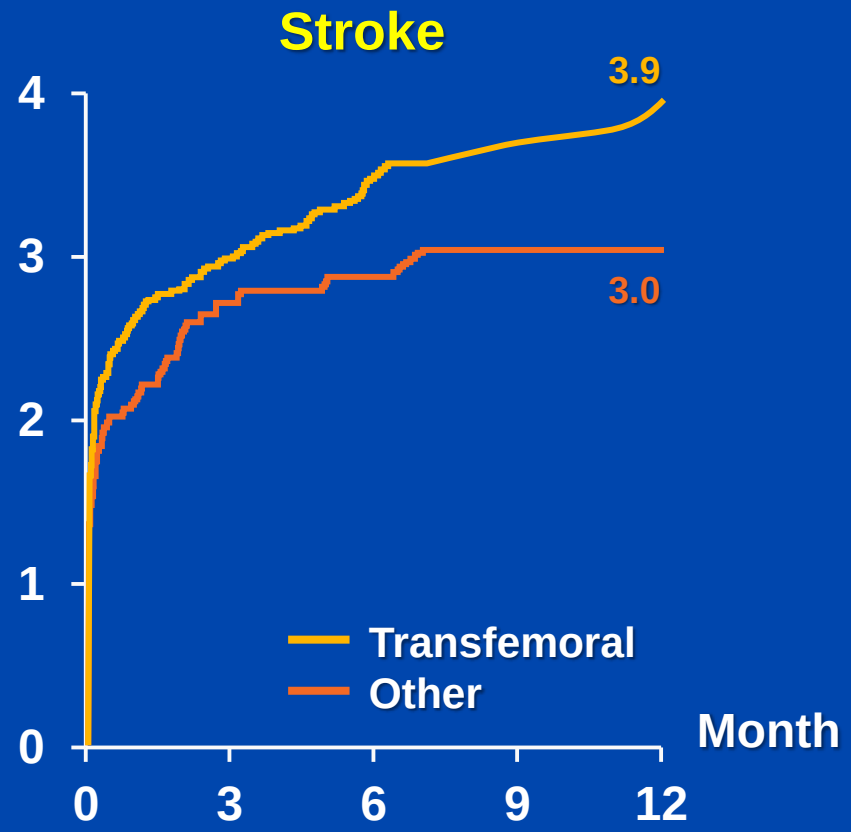
Cumulative Incidence of Death and Stroke
Affect of Access Site





	HR	P
Other vs transfemoral	1.422	<0.001

	HR	P
Other vs transfemoral	0.852	0.346

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TAVR
1 Year Outcomes

	Centers N	Patients N	Death %	Stroke %	Author
TVT/CMS	**230**	**5,980**	**26.2**	**3.6**	**TVT**
PARTNER B	21	179	30.7	11.2	Leon
PARTNER A	25	348	24.3	8.7	Smith
UK TAVI	25	870	21.4	NR	Moat
Canadian TAVI	6	339	24.0	NR	Rodes-Cabau
France 2	33	3,195	24.0	4.1	Gilard
Belgium	15	328	26.0	NR	Bosmans
Pragmatic	4	793	14.3	NR	Chieffo
SOURCE Reg	93	2,706	21.1	7.1	Treede

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Patient Characteristics

Characteristic	Overall Medicare Linked N= 7,825	Study Cohort N= 5,980	Excluded but Medicare linked N= 1,845	P
Age – yr Median (25th, 75th)	84 (79,88)	85 (79, 88)	84 (78, 88)	<0.001
75-84, n (%)	2,991 (38.2)	2,244 (37.5)	747 (40.5)	<0.001
85-94, n (%)	3,664 (46.8)	2,869 (48.0)	795 (43.1)	<0.001
Female, n (%)	3,912 (50.1)	3,006 (50.4)	906 (49.2)	0.365

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Patient Characteristics

Characteristic	Overall Medicare Linked N = 7,825	Study Cohort N = 5,980	Excluded but Medicare linked N = 1,845	P
STS PROM Score (25th, 75th)	7.1 (4.7, 10.8)	7.1 (4.7, 10.9)	6.9 (4.6, 10.5)	0.05
<8% n, (%)	4,501 (57.5)	3,405 (57.0)	1,096 (59.4)	
8-15%	2,401 (30.7)	1,844 (30.8)	557 (30.2)	
>15%	921 (11.8)	729 (12.2)	192 (10.4)	
NYHA Class III/IV Heart Failure, n (%)	6,385 (83.7)	4,876 (83.6)	1,509 (84.2)	
CAD, n (%)	4,719 (62.4)	3,564 (61.7)	1,155 (64.5)	0.039

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Patient Characteristics

Characteristic	Overall Medicare Linked N = 7,825	Study Cohort N = 5,980	Excluded but Medicare linked N = 1,845	P
Prev. Stroke, n (%)	986 (12.6)	764 (12.8)	222 (12.6)	0.395
Peripheral Arterial Disease, n (%)	2,462 (31.5)	1,856 (31.1)	606 (32.9)	0.135
COPD, n (%)				
Severe	1,046 (13.5)	801 (13.5)	245 (13.4)	
Oxygen-dependent lung disease, n (%)	1,132 (14.7)	895 (15.2)	237 (13.0)	0.02

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Patient Characteristics

Characteristic	Overall Medicare Linked N = 7,825	Study Cohort N = 5,980	Excluded but Medicare linked N = 1,845	P
Dialysis dependent	311 (4.0)	249 (4.2)	62 (3.4)	
Serum creatinine <2.0	6,941 (89.1)	5,286 (88.8)	1,655 (90.0)	0.128
5mm walk time >6 sec	2,437 (31.5)	1,796 (30.4)	641 (35.0)	<0.001
LV EF				
<30%, n (%)	545 (7.2)	414 (7.2)	131 (7.4)	
>45%	5,543 (73.3)	4,276 (74.0)	1,267 (71.2)	0.032

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Patient Characteristics

Characteristic	Overall Medicare Linked N = 7,825	Study Cohort N = 5,980	Excluded but Medicare linked N = 1,845	P
Pre-TAVR mitral insufficiency, n (%)				
Moderate	2,098 (31.5)	1,594 (31.2)	504 (32.1)	0.610
Access site				
Transfemoral	4,866 (62.9)	3,770 (63.7)	1,096 (60.3)	0.008
Other	2,868 (37.1)	2,146 (36.3)	722 (39.7)	

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In-Hospital Outcome

Characteristic	Study Cohort N = 5,980	P
In-hospital death	319 (5.3)	0.680
Any in-hospital stroke	99 (1.7)	0.817
Any in-hospital TIA	22 (0.4)	0.324
Any in-hospital valve complication	125 (2.1)	0.951
Conversion to open heart surgery	83 (1.4)	0.561
Discharge location		
Home	3,455 (61.1)	0.002
Extended care/TCU/rehab	1,788 (31.6)	0.002
Other acute care hospital	34 (0.6)	0.002
Nursing home	328 (5.8)	0.002
Hospice	31 (0.5)	0.002
Other	22 (0.4)	0.002

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	Mortality		Stroke	
	HR	P	HR	P
75-84 vs <75	1.224	0.060	0.999	0.998
85-94 vs <75	1.359	0.006	1.160	0.613
95+ vs <75	1.648	0.016	0.289	0.247

	HR	P
75-84 vs <75	1.224	0.060
85-94 vs <75	1.359	0.006
95+ vs <75	1.648	0.016

	HR	P
75-84 vs <75	0.999	0.998
85-94 vs <75	1.160	0.613
95+ vs <75	0.289	0.247

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CoreValve US Pivotal Trial

A Randomized Comparison of Self-expanding Transcatheter and Surgical Aortic Valve Replacement in Patients with Severe Aortic Stenosis Deemed High-Risk for Surgery

David H. Adams, MD
On Behalf of the US CoreValve Investigators

Presenter Disclosure Information

David H. Adams, MD

I receive royalties through the Icahn School of Medicine at Mount Sinai related to intellectual property for mitral and tricuspid valve repair products now owned by Edwards Lifesciences and Medtronic

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Background

Many Patients with Symptomatic Severe Aortic Stenosis are not Ideal Candidates for Surgery due to Increased Risks

- **TAVR with a balloon expandable valve improved survival compared to medical therapy in inoperable patients**
- **TAVR with a balloon expandable valve had similar survival compared to surgery in patients at high risk for surgery**

Leon MB, Smith CR, Mack M, et al: N Engl J Med 2010;363:1597–1607;
Smith CR, Leon MB, Mack M, et al. N Engl J Med 2011;364: 2187–2198

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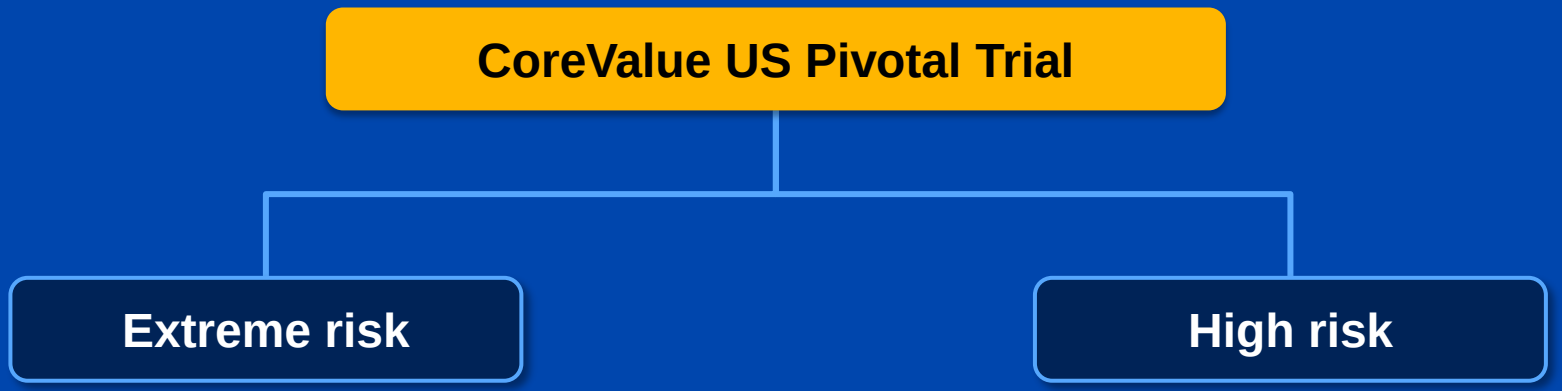
Study Purpose



To assess the safety and effectiveness of TAVR with the CoreValve prosthesis compared to surgical valve replacement in symptomatic patients with severe aortic stenosis at increased surgical risk

Adams DH, Popma JJ, Reardon MJ, et al: New Engl J Med 2014;*in press*

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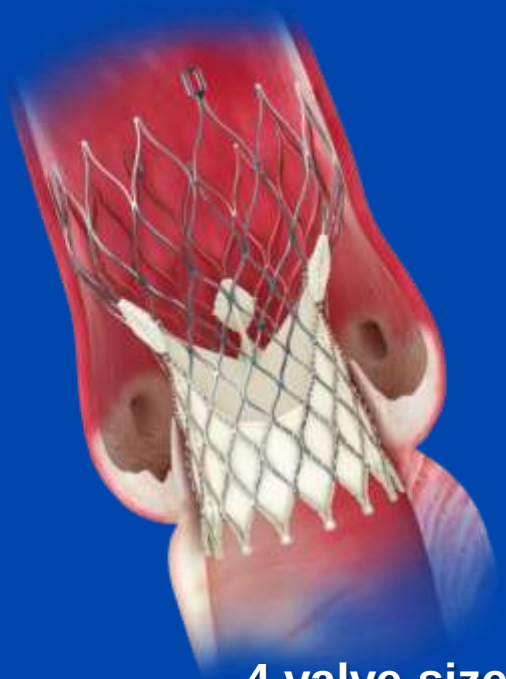
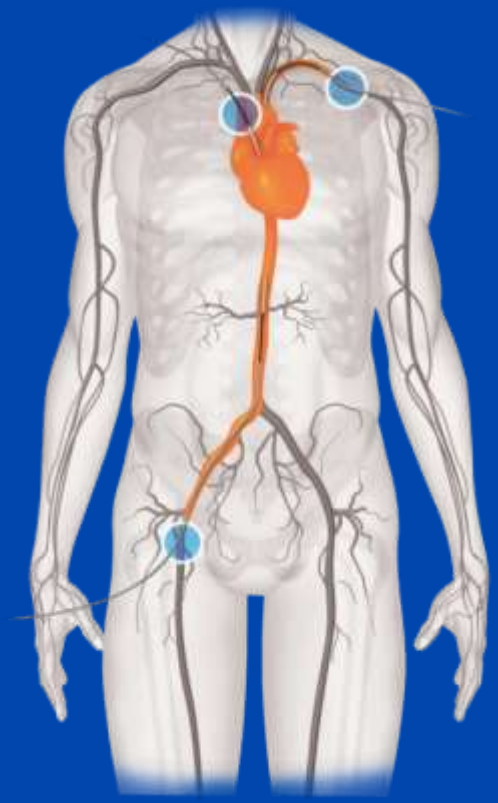
Study Device and Access Routes



4 valve sizes
(18-29 mm annular range)

18Fr delivery system



Transfemoral
subclavian
direct aortic

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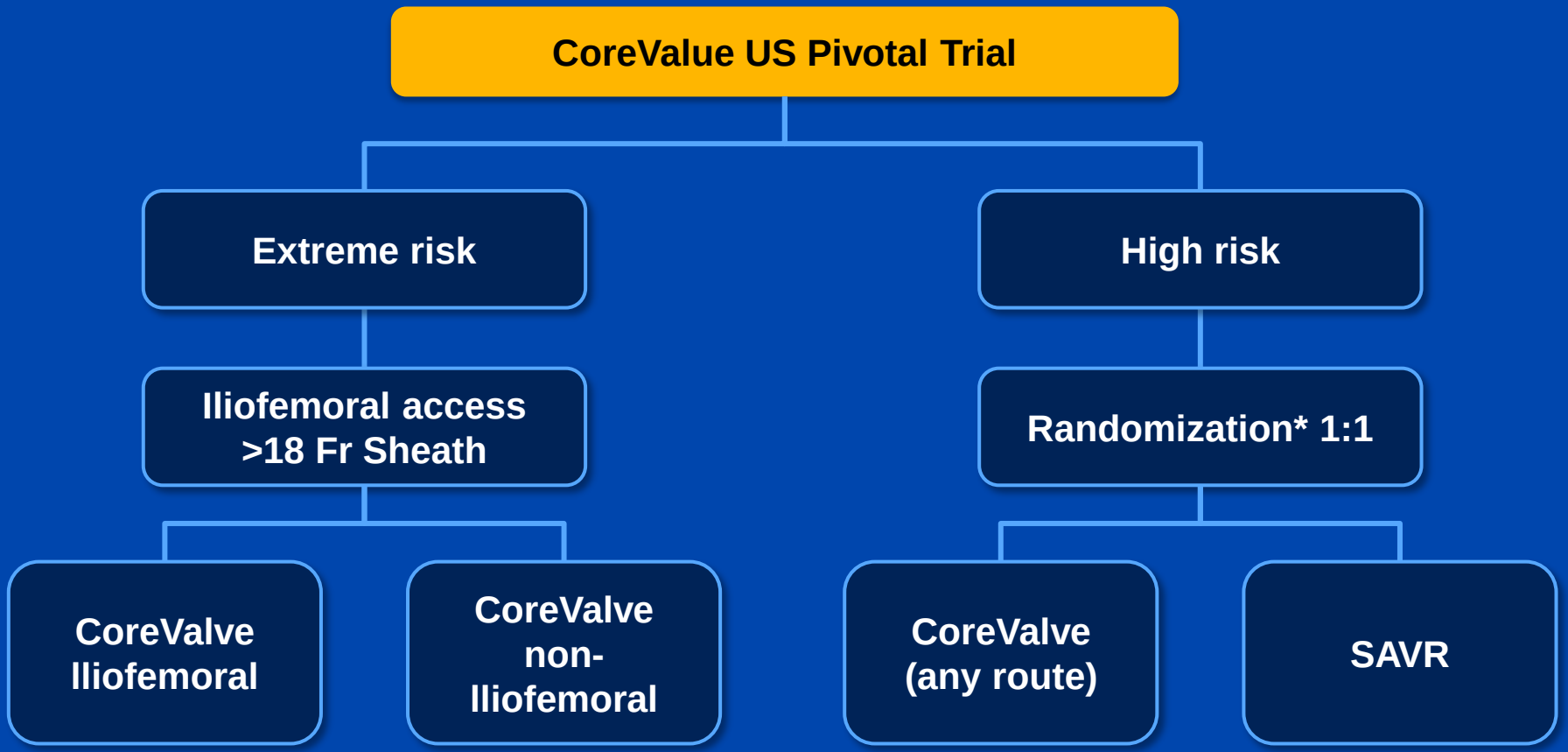
Pivotal Trial Design



*Randomization stratified by intended access site

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Study Administration

Co-Principal Investigators

J. Popma, BIDMC, Boston

D. Adams, Mount Sinai, New York

Steering Committee

CS's: M. Reardon, G.M. Deeb, J. Coselli, D. Adams, T. Gleason

IC's: J. Hermiller, S. Yakubov, M. Buchbinder, J. Popma

Consultants: B. Carabello, P. Serruys

Screening Committee

Chair: M. Reardon, D. Adams, J. Conte, G.M. Deeb, T. Gleason, J. Popma, S. Yakubov

ECG Core Laboratory

Chair: P. Zimetbaum, HCRI

Echo Core Laboratory

Chair: J. Oh, Mayo Clinic

Clinical Events Committee

Chair: D. Cutlip, HCRI

Data & Safety Monitoring Board

Chair: D. Faxon, Brigham and Women's Hospital

Quality of Life and Cost-Effective Assessments

Chair: D. Cohen, Mid-America Heart Institute

M. Reynolds, HCRI

Pathology Core Laboratory

Chair: R. Virmani, CV Path

Rotational X-ray Core Laboratory

Chair: P. Genereux, CRF

Sponsor

Medtronic, Inc.

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Primary Endpoint

Primary Endpoint: All-cause mortality at 1 year

- Non-inferiority Testing: TAVR with the CoreValve prosthesis was non-inferior to SAVR for 1 year all-cause mortality with a 7.5% non-inferiority margin
- Superiority Testing: If the primary endpoint was met at the one-sided 0.05 level, a subsequent test for superiority was performed at the one-sided 0.05 level

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Secondary Endpoints

- Hierarchical Testing of Secondary Endpoints
- Δ mean gradient baseline to 1 year (non-inferior)
- Δ effective orifice area baseline to 1 year (non-inferior)
- Δ NYHA class baseline to 1 year (non-inferior)
- Δ KCCQ baseline to 1 year (non-inferior)
- Difference in MACCE* rate at hospital discharge or 30 days, whichever is later (superiority)
- Δ SF-12 baseline to 30 days (inequality)

*Major adverse cardiovascular and cerebrovascular events, defined as a composite of all-cause mortality, myocardial infarction, all stroke, or aortic-valve reintervention

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Sample Size Determination

- **Hypothesis:** TAVR with the CoreValve prosthesis is non-inferior (7.5% margin) to SAVR in 1 year all-cause mortality
  - H_0: $\pi_{MCS\ TAVR} \geq \pi_{SAVR} + 7.5\%$
  - H_A: $\pi_{MCS\ TAVR} < \pi_{SAVR} + 7.5\%$
- **Sample Size Determination:**
  - 1:1 treatment allocation
  - One-sided alpha = 0.05

  $\pi_{SAVR} = 20\%$

  $\pi_{MCS\ TAVR} = 20\%$
- Power ≥80%

  10% attrition rate
- **Study Size:** 790 patients for a minimum of 355 patients in each arm

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Participating Sites

795 Patients Enrolled at 45 Participating Sites

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Clinical Sites ≥20
High Risk Enrollments

Methodist DeBakey Heart & Vascular Houston, TX N. Kleiman, M. Reardon	42	**Kaiser Permanente – Los Angeles** Los Angeles, CA V. Aharonian, T. Pfeffer	27
University of Michigan Health Systems Ann Arbor, MI S. Chetcuti, G.M. Deeb	39	**The Johns Hopkins Hospital** Baltimore, MD J. Conte, J. Resar	26
Spectrum Health Hospitals Grand Rapids, MI J. Heiser, W. Merhi	38	**Saint Luke's Episcopal Hospital** Houston, TX J. Coselli, J. Diez	25
University of Kansas Hospital Kansas City, KS P. Tadros, G. Zorn	35	**Aurora St. Luke's Medical Center** Milwaukee, WI T. Bajwa, D. O'Hair	24
St. Francis Hospital Roslyn, NY G. Petrossian, N. Robinson	32	**St. Vincent Heart Center of Indiana** Indianapolis, IN D. Heimansohn, J. Hermiller	23
Duke University Medical Center Durham, NC K. Harrison, C. Hughes	30	**Mercy Medical Center** Des Moines, IA A. Chawla, D. Hockmuth	22
Harrisburg Hospital Wormleysburg, PA B. Maini, M. Mumtaz	28	**Banner Good Samaritan** Phoenix, AZ T. Byrne, M. Caskey	22
University of Pittsburgh Pittsburgh, PA T. Gleason, J. Lee	28	**Riverside Methodist Hospital** Columbus, OH D. Watson, S. Yakubov	20

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Inclusion Criteria

- Risk of death at 30 days after surgery was ≥15% and the risk of death or irreversible complications within 30 days was <50%
- Surgical risk assessment included consideration of STS Predicted Risk of Mortality estimate and other risk factors not captured in the STS risk model

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Exclusion Criteria

Clinical and Anatomic Exclusion Criteria Included:

- Recent active GI bleed (<3 mos), stroke (<6 mos), or MI (≤30 days)
- Any interventional procedure with bare metal stents (<30 days) and drug eluting stents (<6 months)
- Creatinine clearance <20 mL/min
- Significant untreated coronary artery disease
- LVEF < 20%
- Life expectancy <1 year due to co-morbidities

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National Screening Committee

- Chairman: Michael J. Reardon, M.D.
- Two clinical site cardiac surgeons and one interventional cardiologist determined patient eligibility
- All patients were reviewed on web-based conference calls with site investigators to confirm eligibility and access route
- Detailed portfolio included
  - STS PROM and all other risk factors
  - Independent review of transthoracic echocardiogram
  - Independent review of chest/abdominal CTA findings
- Two senior surgeons and one cardiologist on the screening committee had to concur with the local heart team assessment to qualify the patient for trial enrollment

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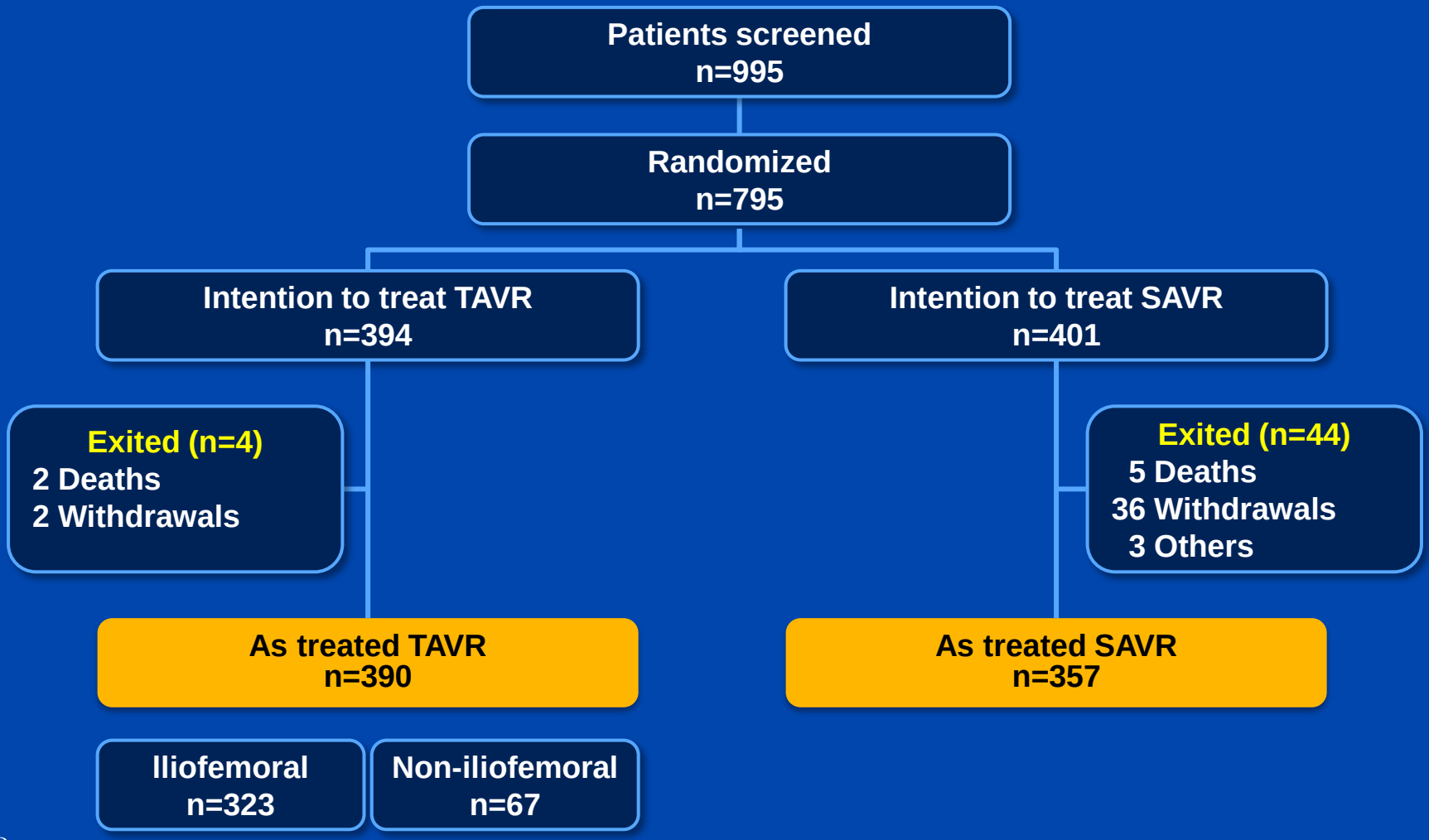
Study Disposition



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Primary Analysis Cohort

As Treated

All randomized patients with an attempted implant procedure, defined as when the patient is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed

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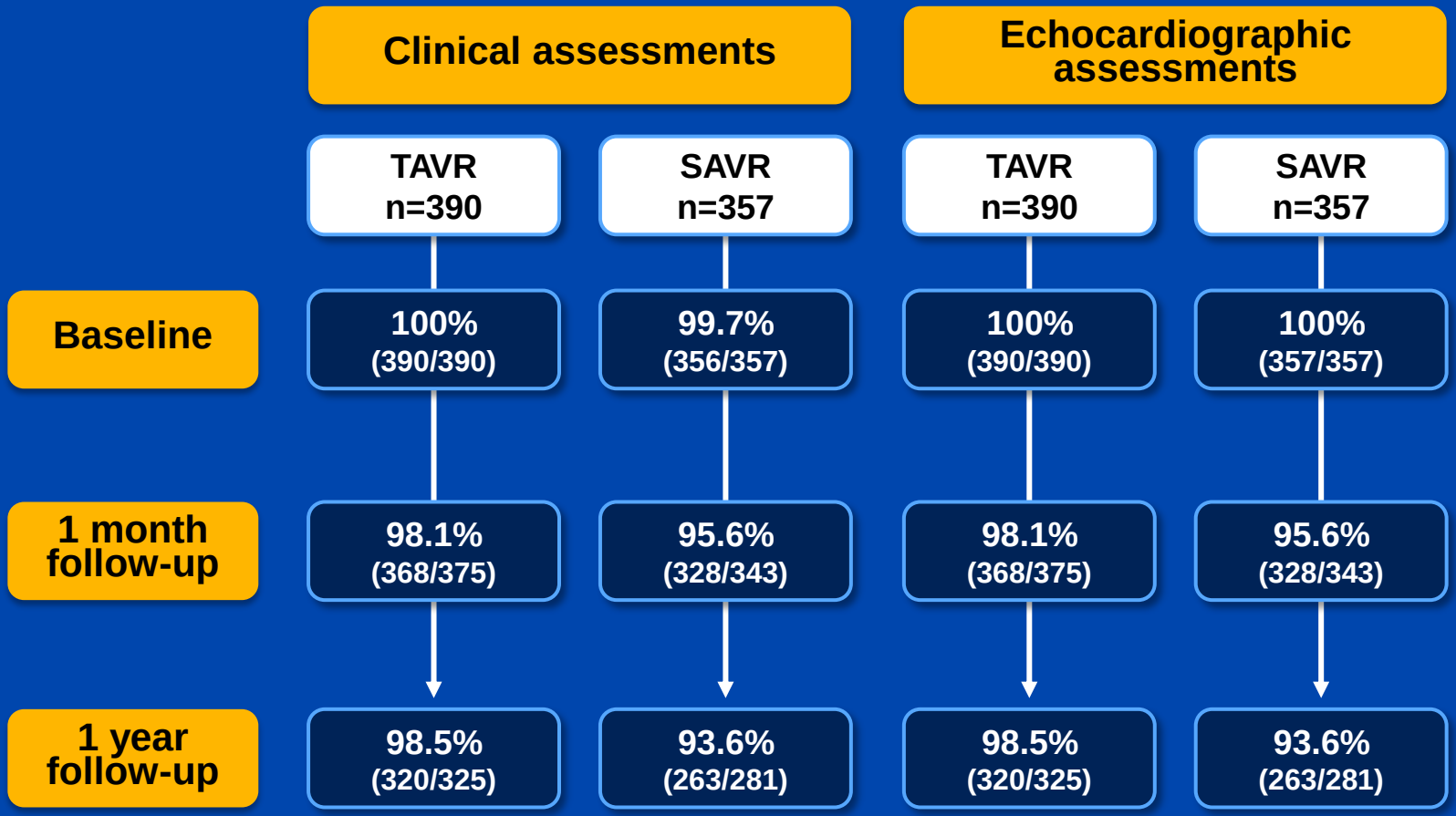
Study Compliance



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Baseline Demographics

Characteristic (%)	TAVR n=390	SAVR N=357
Age, years	83.1±7.1	83.2±6.4
Men	53.1	52.4
STS predicted risk of mortality	7.3±3.0	7.5±3.4
Logistic EuroSCORE	17.7±13.1	18.6±13.0
NYHA class III/IV	85.6	86.8
Diabetes mellitus	34.9*	45.4*
Insulin requiring diabetes	11.0	13.2
Prior stroke	12.6	14.0
Modified Rankin 0 or 1	74.5	87.2
Modified Rankin >1.1	25.5	12.8
STS severe chronic lung disease	13.3	9.0

*P<0.01

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Non-STS Co-Morbidity, Frailty, Disability

Assessment (%)	TAVR n=390	SAVR n=357
Home oxygen	12.9	11.5
Liver cirrhosis	2.6	2.0
Anemia with prior transfusion	18.2	15.9
Immunosuppressive therapy	10.5	8.5
Severe (>5) Charlson Co-Morbidity*	54.1	57.9
Falls in past 6 months	18.5	18.2
5 meter gait speed >6 secs	79.3	80.4
Assisted living	9.7	10.9
Katz ≥1 ADLs deficits	10.5	12.3

*Charlson score: = 1 MI, CHF, PVD, CVD, dementia, chronic lung disease, connective tissue disease, ulcer, mild liver disease, DM; = 2 hemiplegia, mod-severe kidney disease, diabetes with end organ damage, leukemia, lymphoma; = 3 moderate or severe liver disease; = 6 metastatic solid tumor, AIDS

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CoreValve US Pivotal Trial
High Risk Results

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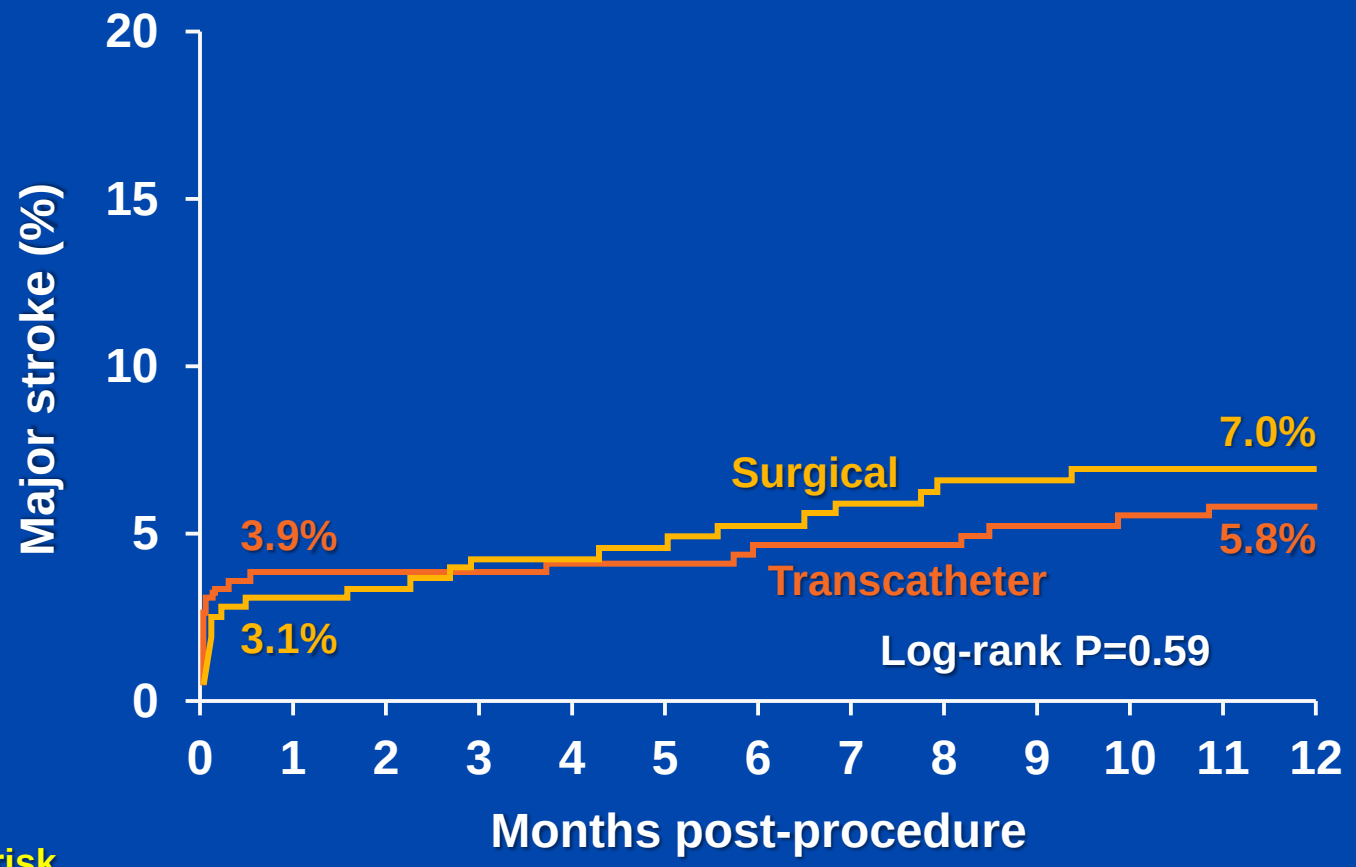
Major Stroke



No. at risk					
Surgical	357	333	289		263
Transcatheter	390	367	344		322

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Secondary Endpoints

Hierarchical Testing of Secondary Endpoints

- Δ mean gradient baseline to 1 year (non-inferior; P<0.001)
- Δ effective orifice area baseline to 1 year (non-inferior; P<0.001)
- Δ NYHA class baseline to 1 year (non-inferior; P<0.001)
- Δ KCCQ baseline to 1 year (non-inferior; P=0.006)
- Difference in MACCE rate at hospital discharge or 30 days, whichever is later (superiority; P=0.103)
- Δ SF-12 baseline to 30 days (inequality; nominal P<0.001)

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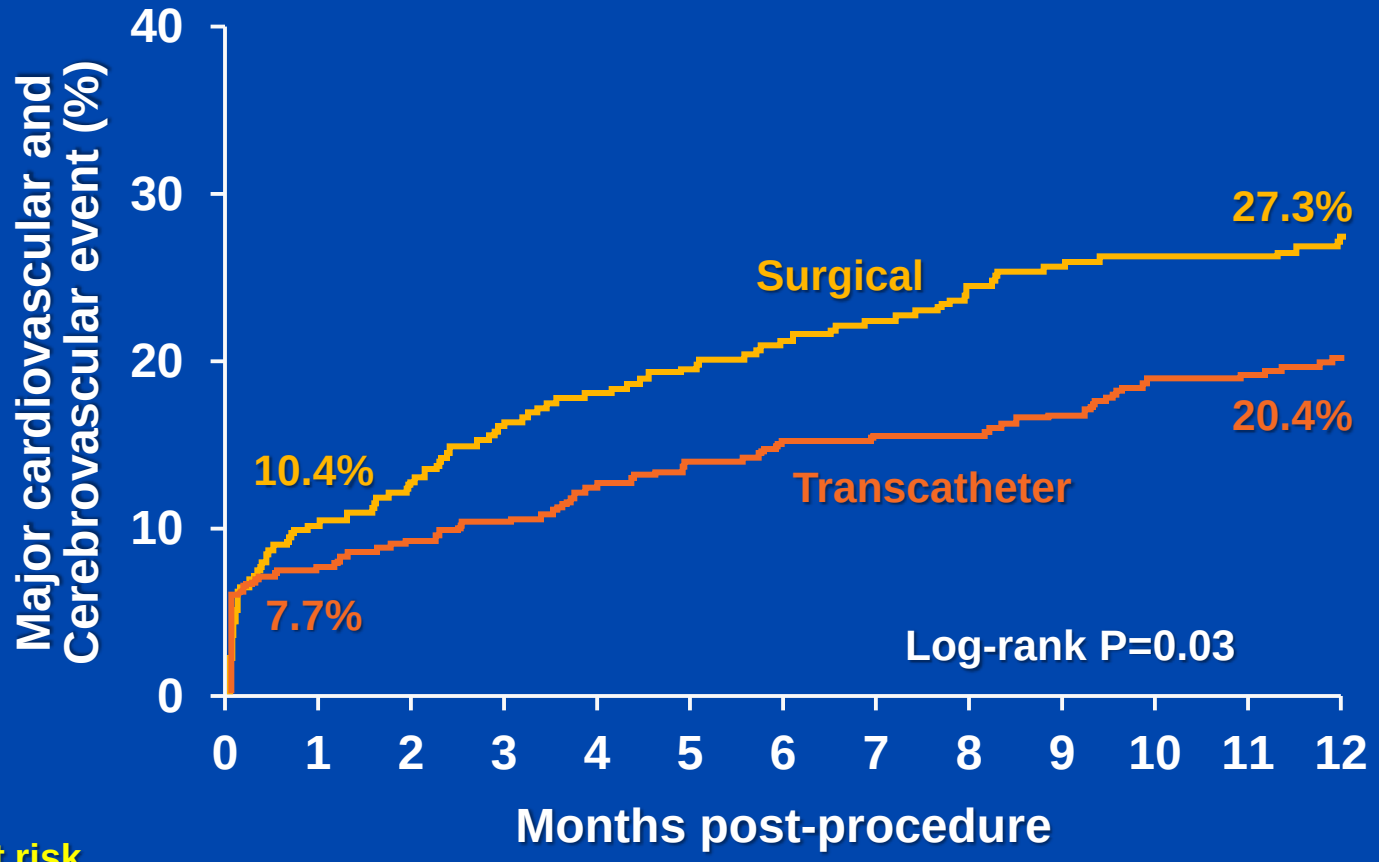
1-Year MACCE



No. at risk					
Surgical	357	320	273		247
Transcatheter	390	360	329		306

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Other Endpoints

	1-month			1-Year		
Events* (%)	TAVR	SAVR	P	TAVR	SAVR	P
Vascular complications (major)	5.9	1.7	0.003	6.2	2.0	0.004
Pacemaker implant	19.8	7.1	<0.001	22.3	11.3	<0.001
Bleeding (life threatening or disabling)	13.6	35.0	<0.001	16.6	38.4	<0.001
New onset or worsening atrial fibrillation	11.7	30.5	<0.001	15.9	32.7	<0.001
Acute kidney injury	6.0	15.1	<0.001	6.0	15.1	<0.001

*Percentages reported are Kaplan-Meier estimates and log-rank P values

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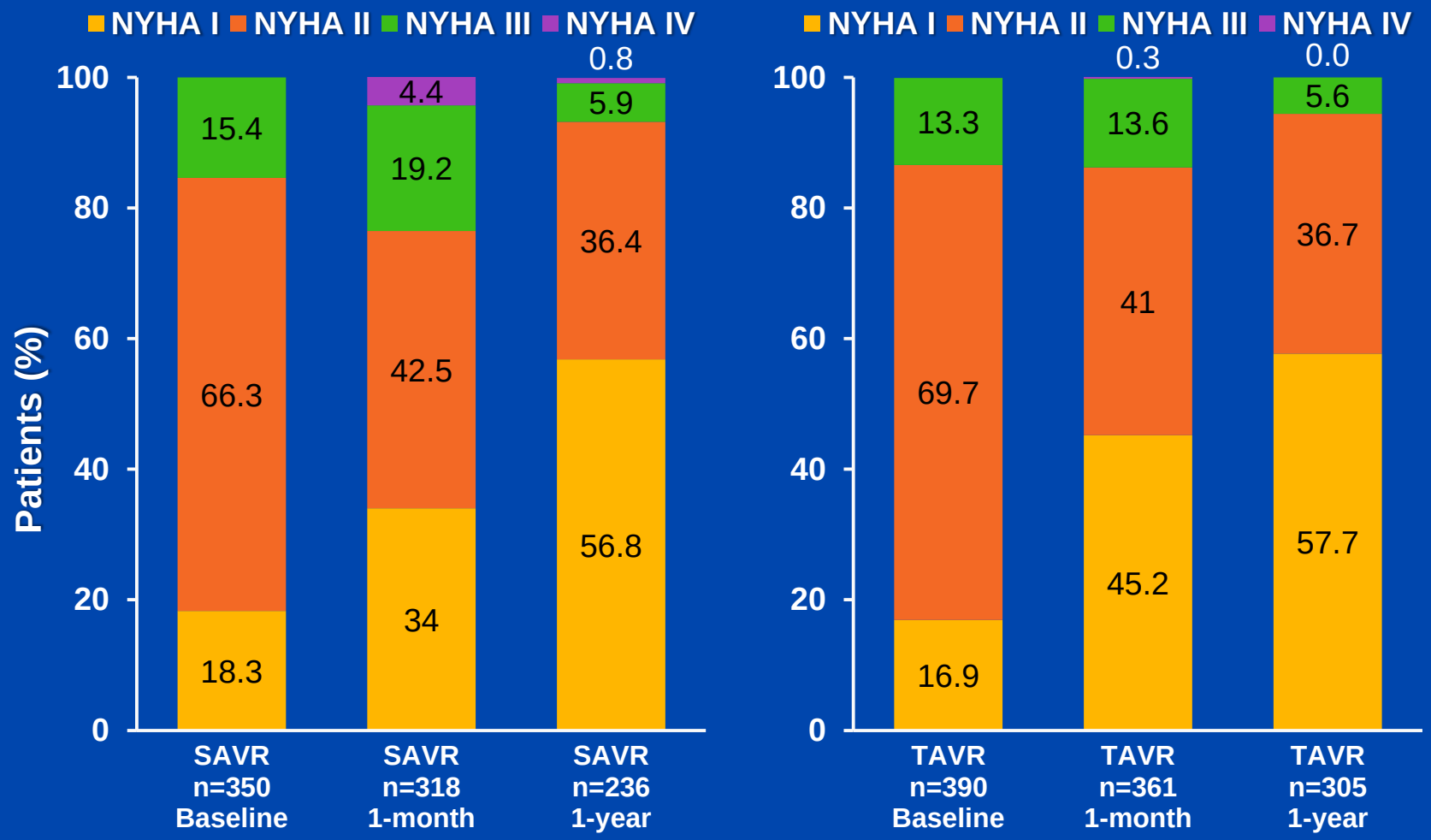
NYHA Class Survivors



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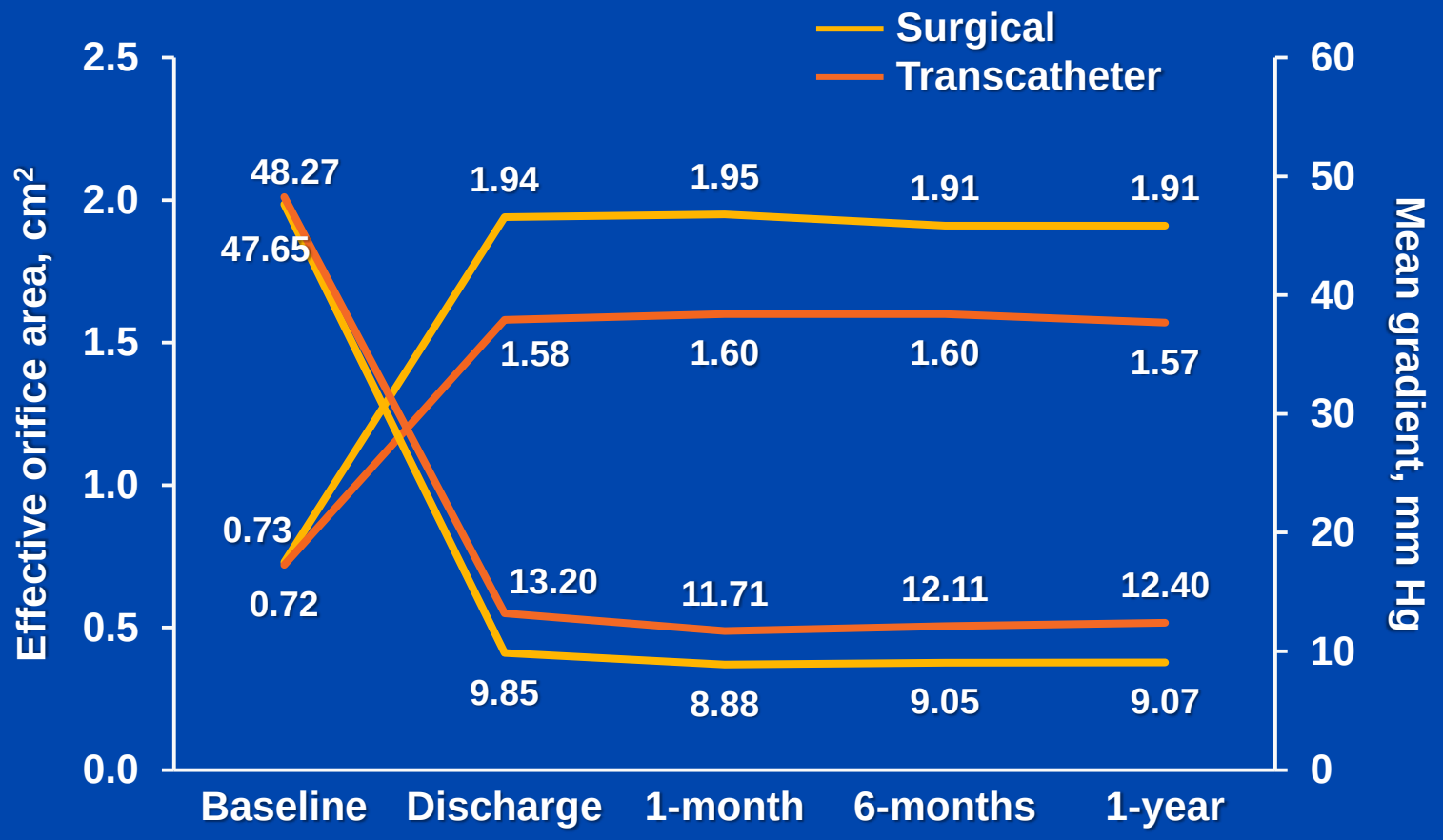
Echocardiographic Findings



Post implant, there were significant differences (P<0.001) between TAVR and SAVR at each time point for both EOA and mean gradient

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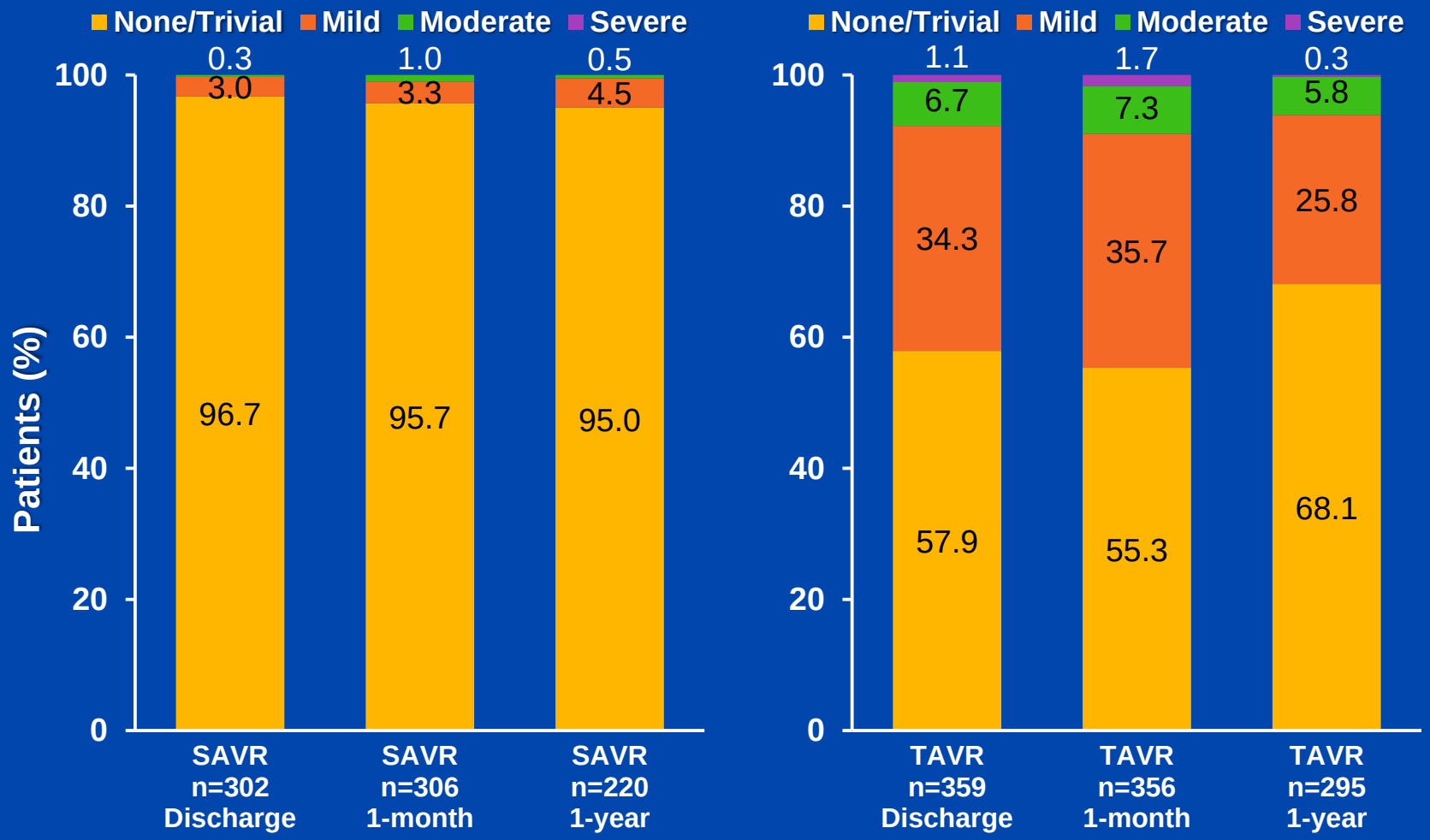
Paravalvular Regurgitation



There was significantly lower PVL with SAVR over TAVR at each time point (P<0.001)

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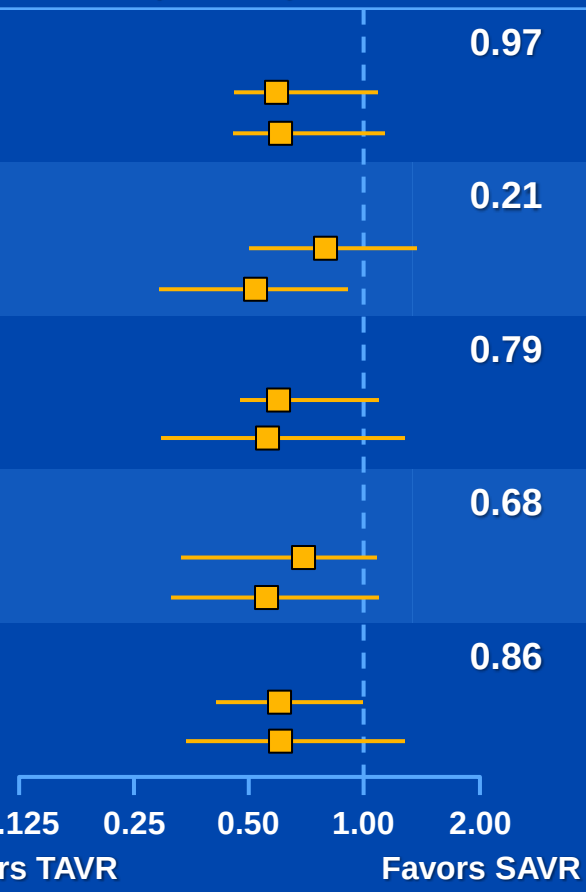
Subgroup Analysis for 1-Year Mortality

Subgroup	All-cause death at 1-year K-M rates: TAVR	All-cause death at 1-year K-M rates: SAVR	Hazard ratios (95% CI)	P
Age				0.97
>85	15.7	21.4	0.71 (0.43, 1.16)	
≤85	12.9	17.2	0.72 (0.43, 1.20)	
Gender				0.21
Male	15.5	16.7	0.89 (0.55, 1.47)	
Female	12.7	21.8	0.56 (0.33, 0.95)	
BMI				0.79
≤30	15.7	20.6	0.73 (0.48, 1.09)	
<30	10.3	15.8	0.64 (0.30, 1.38)	
LVEF				0.68
≤60	15.8	19.9	0.76 (0.49, 1.16)	
<60	11.6	17.8	0.64 (0.34, 1.22)	
Diabetes				0.86
No	15.8	22.3	0.67 (0.44, 1.03)	
Yes	11.3	15.3	0.72 (0.38, 1.37)	



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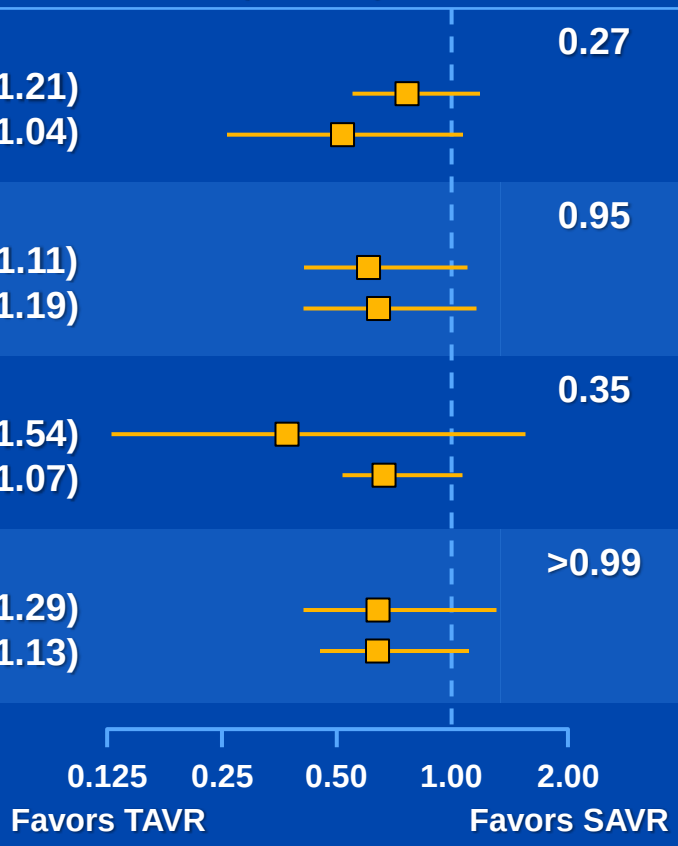
Subgroup Analysis for 1-Year Mortality

Subgroup	All-cause death at 1-year K-M rates: TAVR	All-cause death at 1-year K-M rates: SAVR	Hazard ratios (95% CI)	P
Prior				0.27
No	16.2	19.6	0.80 (0.53, 1.21)	
Yes	9.6	18.1	0.50 (0.24, 1.04)	
PVD				0.95
No	12.8	17.8	0.68 (0.42, 1.11)	
Yes	15.3	21.2	0.70 (0.41, 1.19)	
Hypertension				0.35
No	15.8	36.5	0.37 (0.09, 1.54)	
Yes	14.1	18.4	0.74 (0.51, 1.07)	
STS Score				>0.99
≤7%	10.5	14.2	0.72 (0.40, 1.29)	
>7%	18.2	24.1	0.72 (0.46, 1.13)	



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Limitations

- More patients refused surgical replacement after randomization assignment than refused transcatheter replacement (there were no important differences between treated and withdrawn patients)
- Patients had a lower 30-day mortality rate than was specified in our study inclusion criteria, and therefore the trial population may have been at lower risk than was intended

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Thank You

On Behalf of the U.S. CoreValve Investigators

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Questions & Discussion

Background

- Transcatheter aortic valve replacement is an effective treatment option for high-risk patients with severe aortic stenosis
- Different from surgery, TAVR requires either a balloon-expandable of self-expandable system
- 2 device types are in widespread use
  - Balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences)
  - Self-expandable Medtronic CoreValve (Medtronic Inc.)

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Background

- Some observational registries have reported a lower frequency of post-procedural paravalvular aortic regurgitation with the balloon-expandable device*
- However, recent improvements in pre-procedural imaging and device size selection, refinements in implantation technique, and the recognition of paravalvular leaks as a relevant clinical complication, might affect the functional outcome of both valves
- A randomized comparison of both device is lacking

*Moat et al: JACC, 2011; Gilard et al: NEJM, 2012; Nombela-Franco et al: AJC, 2013; Abdel-Wahab et al: JACC Cardiovasc Interv, 2014

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Purpose of CHOICE

To compare the performance of balloon expandable and self-expandable transcatheter aortic valves regarding overall device success in a randomized clinical trial for patients with symptomatic severe aortic stenosis at high-risk for surgery

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Inclusion and Exclusion Criteria

- Main inclusion criteria
  - Severe symptomatic aortic stenosis (aortic valve area ≤1 cm^2 or 0.6 cm^2/m^2)
  - High risk for surgery (age >75 years and/or Logistic EuroSCORE ≥2% and/or STS risk score ≥10% and/or contraindication to conventional surgical replacement)
  - Native aortic valve annulus measuring 20-27 mm
  - Suitable transfemoral vascular access
- Main exclusion criteria
  - Native aortic valve annulus <20 mm and >27 mm
  - Pre-existing aortic bioprosthesis
  - Cardiogenic shock or hemodynamic instability

*Moat et al: JACC, 2011; Gilard et al: NEJM, 2012; Nombela-Franco et al: AJC, 2013; Abdel-Wahab et al: JACC Cardiovasc Interv, 2014

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Primary Endpoint

- 'Device success' (first VARC definition), which is a 'technical' composite endpoint including
  - Successful vascular access, delivery and deployment of the device and retrieval of the delivery system
  - Correct position of the device in the proper anatomical location
  - Intended performance of the prosthetic heart valve(aortic valve area >1.2 cm^2 and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, without moderate or severe prosthetic valve AR)
  - Only one valve implanted in the proper anatomical location
- Power calculation
  - The assumed incidence of device success was 70% with the self-expandable valve and 85% with the balloon-expandable valve*
  - Power of 80%, alpha level of 0.05
  - The calculated sample size was a total of 240 patients, 120 patients per group

*Moat et al: JACC, 2011; Gilard et al: NEJM, 2012; Nombela-Franco et al: AJC, 2013; Abdel-Wahab et al: JACC Cardiovasc Interv, 2014

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30-Day Secondary Endpoints*

- Cardiovascular mortality
- Major and minor vascular complications
- Major and minor bleeding
- Post-procedural pacemaker implantation
- NYHA class improvement (by at least 1 functional class)
- Combined safety endpoint
  - A composite of all cause mortality, major stroke, life threatening or disabling bleeding, acute kidney injury stage 3 including renal replacement therapy, peri-procedural myocardial infarction, major vascular complications and repeat procedure for valve-related dysfunction)
- Major adverse cardiovascular and cerebrovascular events
  - A composite of myocardial infarction, cardiac or vascular surgery and stroke

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*Endpoints defined according to VARC 1
Further follow-up is planned at 6 months, 1 year, 2 and 5 years

Study Methodology

- Device size selection was based on manufacture's sizing charts, but the steering committee strongly recommended sizing to be based on 3-D imaging
  - MDCT-based annular are for the balloon-expandable valve
  - MDCT-based annular perimeter for the self-expandable valve
- All procedure were performed by experienced operators in centers with an established multidisciplinary TAVR program
- The procedure was mainly performed under analgo-sedation using fluoroscopic guidance (TEE only in selected cases)

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Assessment of Aortic Regurgitation

- Assessment of AR after implantation was performing using
  1. Angiography (standardization acquisition, core-lab adjudicated)
  2. Transthoracic echocardiography (VARC 1 criteria)
  3. Invasive hemodynamic measurements (AR Index)
- Assessment of valve function at follow-up was performed using
  1. Transthoracic echocardiography (48 hours, 30 days, and will be further assessed at intermediate and long-term follow-up)
  2. Cardiac MRI in a subgroup of patients (7-14 days and 6 months after TAVR)
- Assessment of post-procedural AR as a criterion of the primary endpoint was performed using core-lab angiography

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Study Sites and Organization

- Steering Committee
  - G. Richardt
  - M. Abdel-Wahab
- Clinical Endpoints Committee
  - H.-W. Beurich
  - M. Abdel-Wahab
- Data Management
  - Zentrum für Klinische Studien, Bad Segeberg, Germany
- Data Safety and Monitoring Board
  - E.-G. Kraatz (chair)
- Angiographic core lab
  - D. R. Robinson, University of Sussex, Brighton, England
- Funding
  - Heart Center, Segeberger Klinken GmbH, Bad Segeberg, Germany

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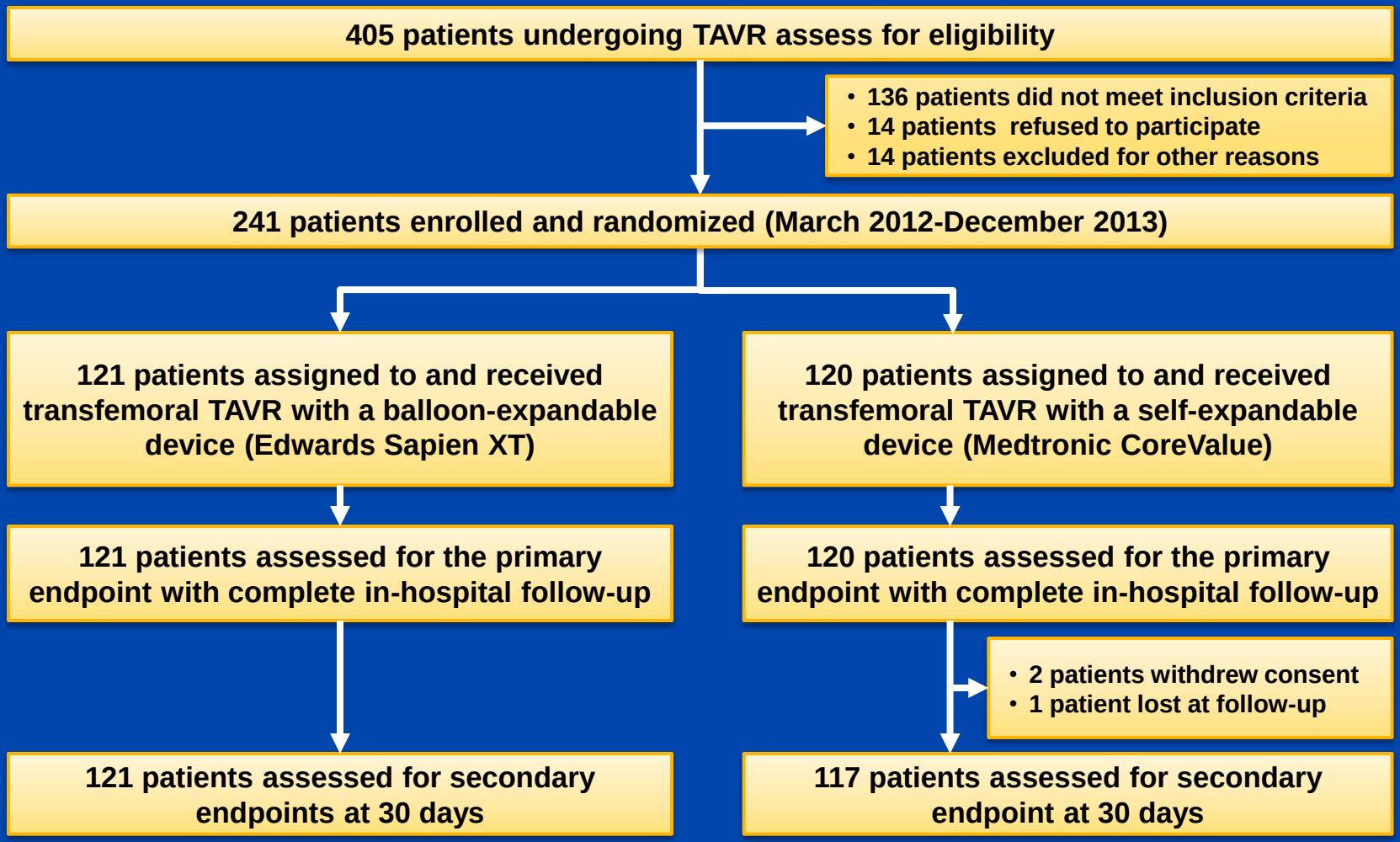
Study Flow



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Baseline Characteristics
Demographics

	Balloon-expandable (n=121)	Self-expandable (n=120)	P
Age (years)	81.9±6.7	79.6±15.8	0.14
Females	69/121 (57%)	86/120 (71.7%)	0.02
BMI (kg/m^2)	26.4±4.2	26.6±5.2	0.77
Logistic EuroSCORE	21.5±12.9	22.1±14.7	0.72
EuroSCORE II	6.4±6.7	6.2±5.8	0.76
STS score	5.6±2.9	6.2±3.9	0.17
NYHA class III or IV	97/121 (80.2%)	98/120 (81.7%)	0.76

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Baseline Patient Characteristics
Comorbidities

	Balloon-expandable (n=121)	Self-expandable (n=120)	P
Diabetes mellitus	38/121 (31.4%)	32/120 (26.7%)	0.42
CAD	73/121 (60.3%)	79/120 (65.8%)	0.38
Previous CABG	19/121 (15.7%)	15/120 (12.5%)	0.48
Previous PCI	44/121 (36.4%)	51/120 (18.3%)	0.33
Peripheral vascular disease	20/121 (16.5%)	22/120 (18.3%)	0.88
Pulmonary disease	27/121 (22.3%)	24/120 (20.0%)	0.66
Creatinine level (mg/dL)	1.1±0.4	1.2±0.5	0.18
Atrial fibrillation	39/117 (33.3%)	29/117 (24.8%)	0.15
Permanent pacemaker	7/117 (5.9%)	9/117 (7.7%)	0.60

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Baseline Transesophageal Echocardiography

	Balloon-expandable (n=120)	Self-expandable (n=116)	P
AVA (cm^2)	0.7±0.2	0.7±0.2	0.71
Indexed AVA (cm^2/m^2)	0.4±0.1	0.4±0.1	0.34
Mean gradient (mm Hg)	43.3±15.4	43.0±13.9	0.90
LVEF (%)	52.5±13.8	54.9±11.9	0.15
LVEF ≤35%	18/120 (15.0%)	11/115 (9.6%)	0.21
Moderate or severe AR	17/118 (14.4%)	24/115 (20.9%)	0.19
Moderate or severe MR	44/119 (36.9%)	38/116 (32.7%)	0.49
sPAP (mm Hg)	37.3±13.1	39.2±13.6	0.34

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Baseline Transthoracic Echocardiography

	Balloon-expandable (n=120)	Self-expandable (n=116)	P
Annulus diameter (mm)	23.3±2.2	23.1±1.9	0.46
Leaflet calcification			0.60
Moderate	31/106 (29.2%)	33/101 (32.7%)	
Severe	75/106 (70.8%)	68/101 (67.3%)	
Asymmetric calcification	26/94 (27.7%)	26/101 (25.7%)	0.76
Eccentric valve orifice	9/97 (9.3%)	12/100 (12.0%)	0.54
Bicuspid aortic valve	0/107 (0.0%)	0/102 (0.0%)	–

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Baseline Multislice CT

	Balloon-expandable (n=97)	Self-expandable (n=94)	P
Aortic annulus			
Mean diameter (mm)	24.1±1.7	23.6±2.0	0.09
Eccentricity index	0.17±0.06	0.18±0.07	0.75
Leaflet calcification			0.99
Mild	9/94 (9.6%)	20/93 (21.5%)	
Moderate	52/94 (55.3%)	33/93 (35.5%)	
Severe	33/94 (35.1%)	40/93 (43.0%)	
LVOT calcification			0.15
None	45/94 (47.9%)	56/93 (60.2%)	
Mild	21/94 (22.3%)	15/93 (16.1%)	
Moderate	23/94 (24.5%)	16/93 (17.2%)	
Severe	5/94 (5.3%)	6/93 (17.2%)	

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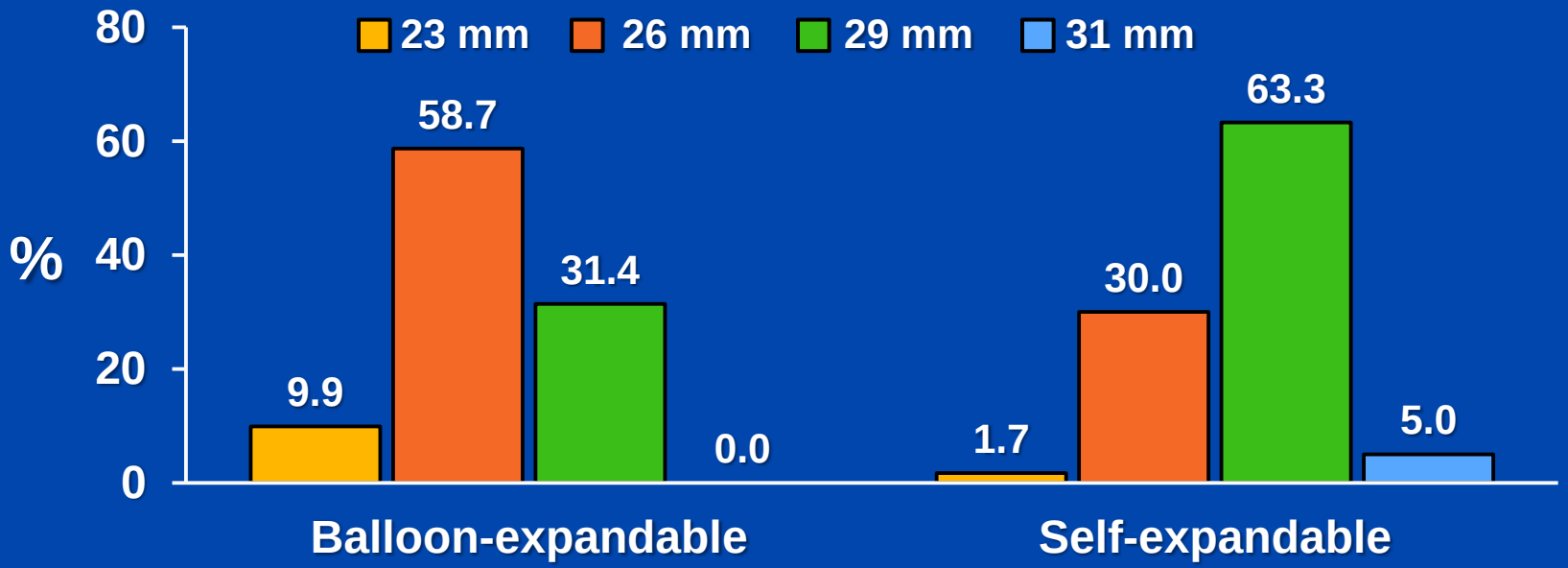
Procedural Factors
Valve Sizes



Percent oversizing	Balloon-expandable	Self-expandable	P
TEE diameter	12.8±5.4	17.7±5.9	<0.001
Mean MDCT diameter	9.6±5.6	15.8±4.5	<0.001
MDCT area	19.5±8.0	30.8±8.2	<0.001
MDCT perimeter	7.2±4.9	14.8±4.9	<0.001

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Procedural Details

	Balloon-expandable (n=121)	Self-expandable (n=120)	P
Balloon pre-dilation	121/121 (100%)	106/120 (88.3%)	<0.001
AR after initial implantation			<0.001
None/trace	72/121 (59.5%)	31/120 (25.8%)	
Mild	34/121 (28.1%)	38/120 (31.7%)	
Moderate	10/121 (8.3%)	33/120 (27.5%)	
Severe	5/121 (4.1%)	18/120 (15.0%)	
Maneuvers to improve AR			
Balloon post-dilation	24/121 (19.8%)	59/120 (49.2%)	<0.001
Valve snaring	0/121 (0.0%)	2/120 (1.7%)	0.24
Implantation of ≥2 valves	1/121 (0.8%)	7/120 (5.8%)	0.03
Coronary obstruction	2/121 (1.6%)	0/120 (0.0%)	0.49
Annular rupture	0/121 (0%)	0/120 (0.0%)	–
Left-to-right shunt	2/121 (1.6%)	2/120 (1.7%)	0.99
Depth of implantation (mm)	–	5.2±3.2	–
Procedural duration (min)	74.5±29.5	80.5±40.5	0.20
Contrast amount (mL)	208.6±71.4	223.1±98.2	0.19

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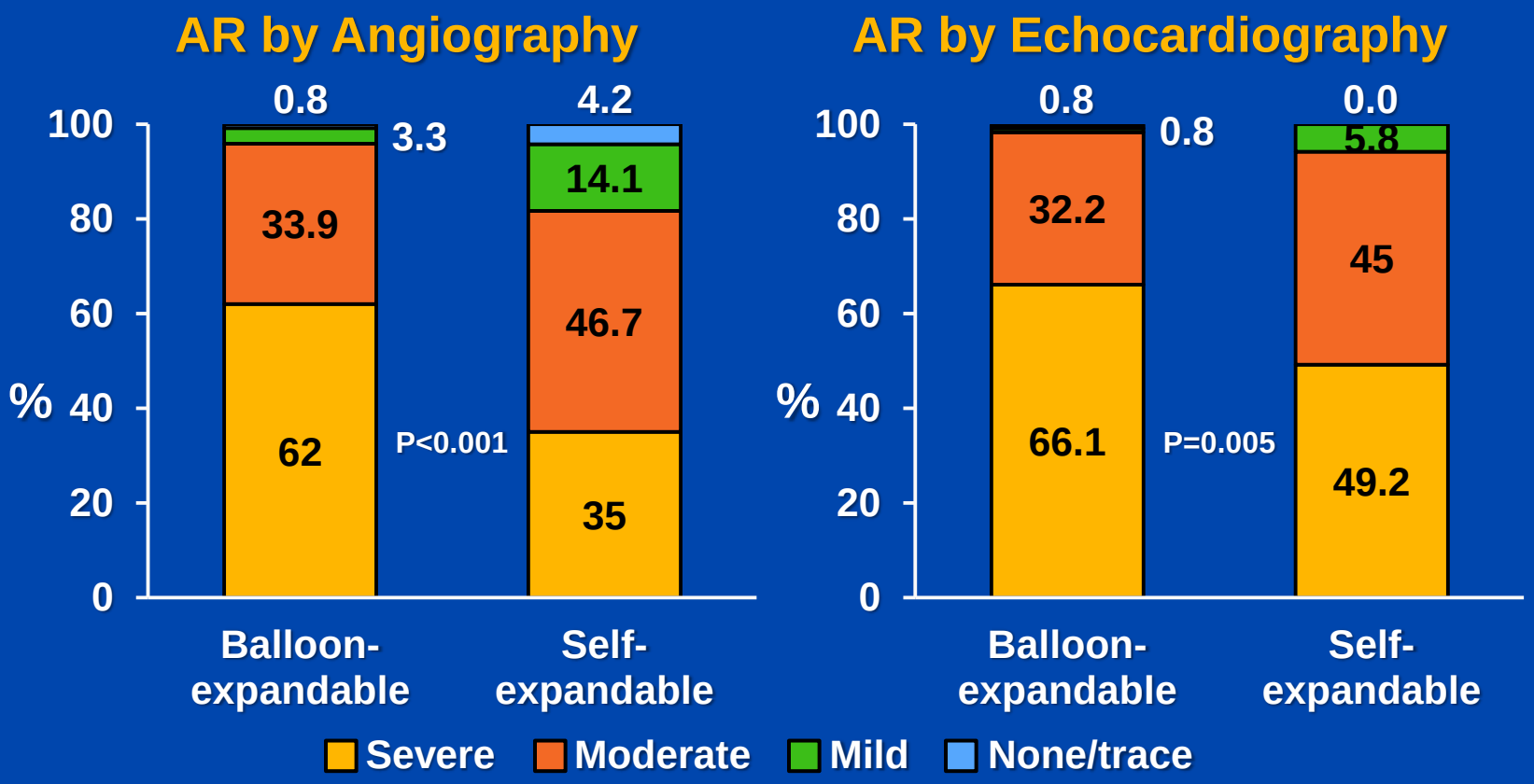
Post-Procedural Aortic Regurgitation



	Balloon-expandable (n=116)	Self-expandable (n=114)	P
Dimensionless AR index	29.0±7.1	27.3±7.2	0.08

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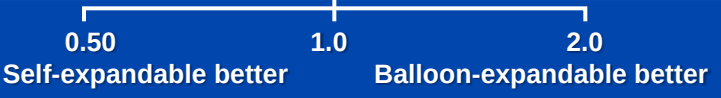
Subgroup Analysis
Relative Risk of Primary Endpoint

	Balloon-expandable (no. of events/total, %)	Self-expandable (no. of events/total, %)	Risk ratio (95% CI)	P
All patients	116/121 (95.9)	93/120 (77.5)	1.24 (1.12-1.37)	
Age				0.89
≥80 years	82/85 (96.5)	62/76 (81.6)	1.18 (1.05-1.33)	
<80 years	34/36 (94.4)	31/44 (70.4)	1.34 (1.09-1.65)	
Gender				0.22
Male	50/52 (96.1)	21/34 (61.8)	1.56 (1.19-2.04)	
Female	66/69 (95.6)	72/86 (83.7)	1.14 (1.03-1.27)	
CAD				0.84
No	47/48 (97.9)	35/41 (85.4)	1.15 (1.00-1.31)	
Yes	69/73 (94.5)	58/79 (73.4)	1.29 (1.12-1.49)	
LVEF				0.95
>35%	97/101 (96.0)	80/100 (80.0)	1.20 (0.94-1.78)	
≤35%	18/19 (94.7)	11/15 (73.3)	1.29 (0.94-1.78)	
Mitral regurgitation				0.70
No/mild	72/75 (96.0)	63/78 (80.8)	1.19 (1.06-1.34)	
Moderate/severe	42/44 (95.5)	27/38 (71.1)	1.34 (1.09-1.66)	
CT annulus diameter				0.23
<25 mm	56/60 (93.3)	55/68 (80.9)	1.15 (1.01-1.32)	
≥25 mm	34/35 (97.1)	18/26 (69.2)	1.40 (1.08-1.82)	
Annular eccentricity				0.37
≤0.25	81/84 (96.4)	60/77 (77.9)	1.24 (1.09-1.40)	
>0.25	8/9 (88.9)	11/14 (78.6)	1.13 (0.79-1.62)	
Leaflet calcification				0.28
No/mild	8/9 (88.9)	17/20 (85.0)	1.04 (0.78-1.41)	
Moderate/severe	81/85 (95.3)	56/73 (76.7)	1.24 (1.09-1.42)	
LVOT calcification				0.15
No/mild	64/66 (97.0)	55/71 (77.5)	1.25 (1.10-1.43)	
Moderate/severe	25/28 (89.3)	18/22 (81.8)	1.09 (0.86-1.38)	



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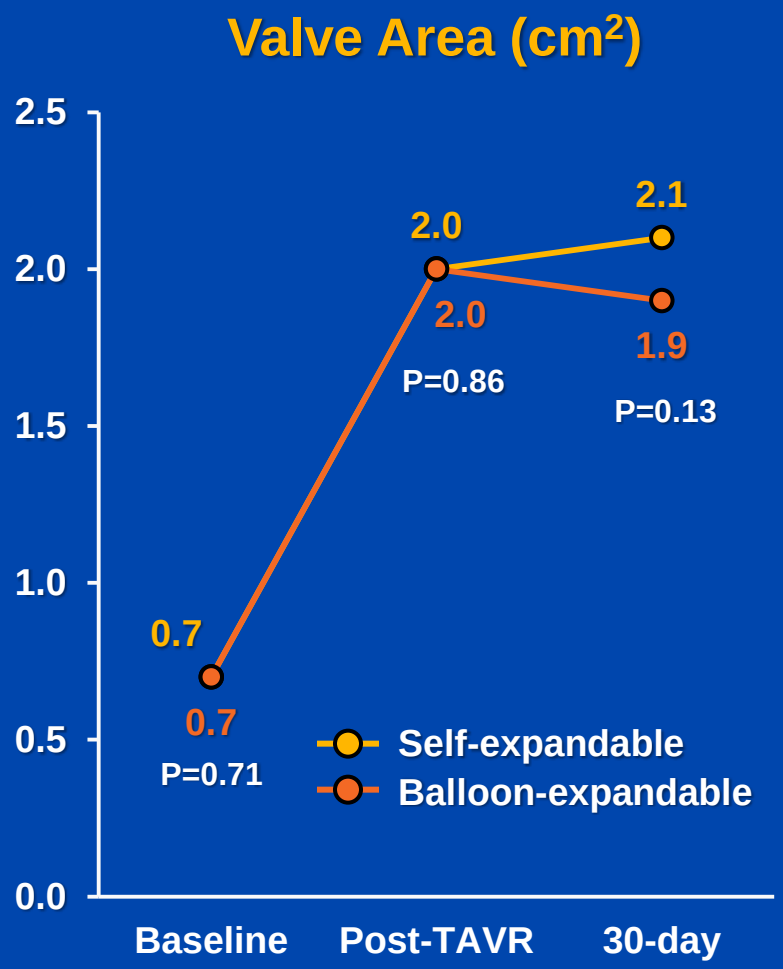
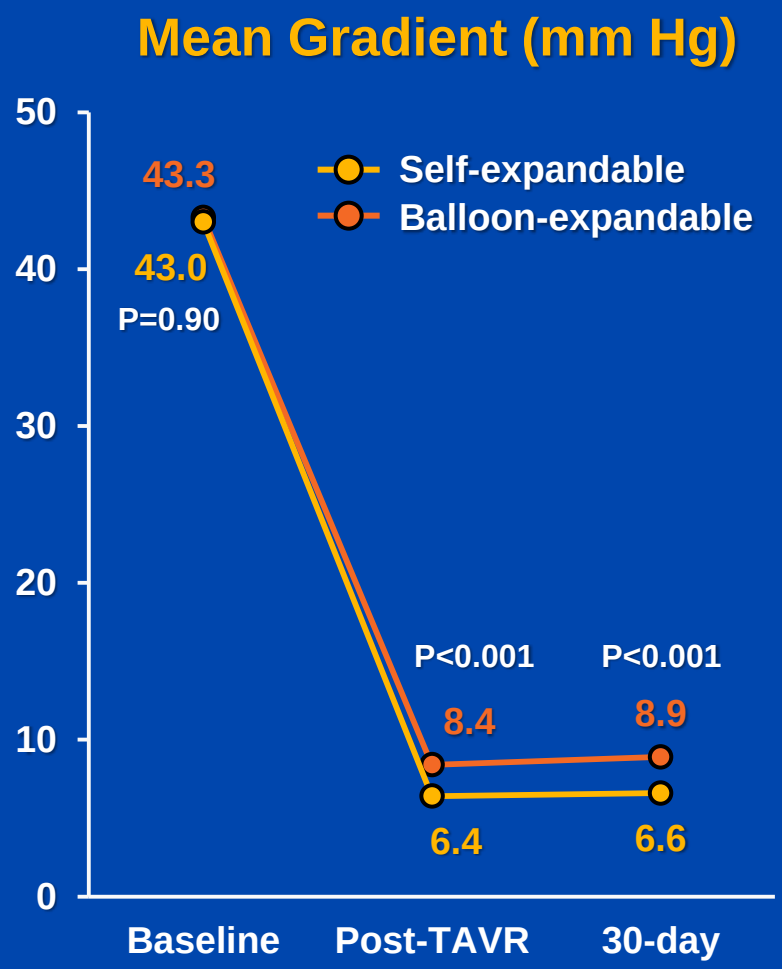
Echocardiographic Findings





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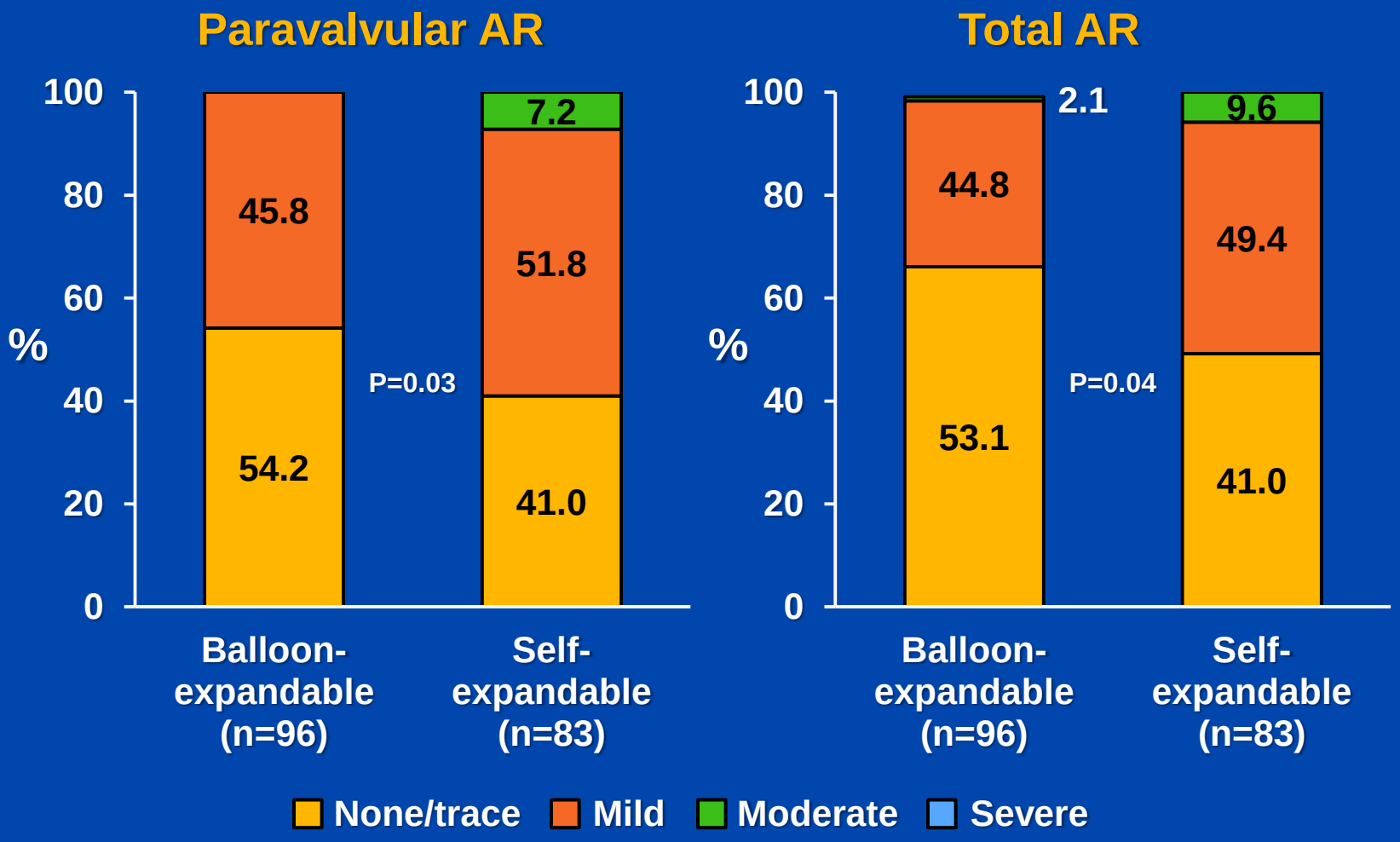
Echocardiographic Findings
Aortic Regurgitation at 30 Days



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Cardiac MRI Subgroup

	Balloon-expandable (n=56)	Self-expandable (n=34)	P
LV ejection fraction (%)	55.6±12.8	56.5±9.8	0.72
Antegrade volume (mL)	70.8±15.0	70.1±17.1	0.84
Retrograde (mL)	2.9±2.9	4.5±6.0	0.21
Regurgitate fraction (%)	4.2±3.9	7.1±8.2	0.06
More-than-mild AR (RF ≥15%)	1/55 (1.8%)	6/33 (18.2%)	0.01

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Study Limitations

- Assessment of AR as a criterion of the primary endpoint using core lab angiography and the lack of an echocardiographic core lab
- However, the following points need to be considered
  - Lack of validation of the VARC echocardiographic grading criteria
  - Possible underestimation of AR severity by echo*
  - Prognostic relevance of angiographic AR at least as strong as echocardiographic AR**
  - The timing, angiographic views, and amount and flow-rate of contrast were standardized
  - The angiographic findings were confirmed by a wide range of assessment tools, including echo, hemodynamic measurements and cardiac MRI

*Sherif et al: EuroIntervention, 2011
**Abdel-Wahab et al: JACC Cardiovasc Interv, 2014

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	SURTAVI COREVALVE	Commercial COREVALVE	S3I SAPIEN 3	Commercial SAPIEN	SAPIEN XT	REPRISE II (LOTUS)	PORTICO-IDE	XL PERCEVAL
								
Date available	Soon	Soon	Now	Now	Soon	Future	Future	Now
Study design	Randomized TAVR vs SAVR	FDA Approved	Registry	FDA Approved	Awaiting FDA	Registry	Randomized PORTICO vs other TAVR	Registry
AVA or AVAI	≤1.0 cm^2 <0.6 cm^2/m^2	≤1.0 cm^2 <0.6 cm^2/m^2	≤0.8 cm^2 <0.5 cm^2/m^2	≤1.0 cm^2 <0.6 cm^2/m^2	<1.0 cm^2 <0.6 cm^2/m^2	<1.0 cm^2	<1.0 cm^2	<1.0 cm^2 <0.6 cm^2/m^2
Peak velocity or mean gradient	≥4 m/s ≥40 mm Hg	≥4 m/s ≥40 mm Hg	≥4 m/s ≥40 mm Hg	≥4 m/s ≥40 mm Hg	≥4 m/s ≥40 mm Hg	≥4 m/s ≥40 mm Hg	≥4 m/s ≥40 mm Hg	≥4 m/s ≥40 mm Hg
STS Risk	4-10%	≥8%	4-8%	≥8%	≥8%	≥8%	≥8%	<8%
TTE annulus dimensions	18-29 mm	18-29 mm	18-28 mm	19-24 mm	18-28 mm	19-27 mm	19-23 mm	19-27 mm
CT annulus area (mm^2)	23: 254.5-314.2 26: 314.2-415.5 29: 415.5-572.6 31: 530.9-660.5	23: 254.5-314.2 26: 314.2-415.5 29: 415.5-572.6 31: 530.9-660.5	23: 338-430 26: 430-546 29: 540-680	23: 300-380 26: 415-490	23: 300-380 26: 415-490 29: 530-620			21: 23: 25:
CT perimeter (mm)	23: 56.5-62.8 26: 62.8-72.3 29: 72.3-81.7 31: 81.7-91.1	23: 56.5-62.8 26: 62.8-72.3 29: 72.3-81.7 31: 81.7-91.1	23: 26: 29:	23: 60-69 26: 72-78.5	23: 60-69 26: 72-78.5 29: 81.5-88			
Minimum iliofemoral diameter for TF (mm)	23-31: 6.0	23-31: 6.0	23: 5.5 26: 5.5 29: 6.0	23: 7.0 26: 8.0	23: 6.0 26: 6.5 29: 7.0			NA

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Last updated 4/6/2014 MFE
source: clinicaltrials.gov

Important Exclusion Criteria for SURTAVI

- True porcelain aorta
- Life expectancy <2 years
- Extensive mediastinal irradiation
- Child Class C Cirrhosis
- ESRD on HD or CrCl <20
- Severe Pulmonary Hypertension (PASP >80)
- Severe COPD with FEV1 <750 cc
- Any valve prosthesis, severe MR, MS or TR
- Vascular anatomy not able to accommodate 18F sheath

*No recent peripheral vascular interventional procedure with last 30 days prior to randomization

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Frailty Exclusion Criteria for SURTAVI

Frailty assessments identify

- Subject is <80 years of age and 3 or more of the following apply
- Subject is ≥80 years of age and two or more of the following apply
  - Wheelchair bound
  - Resides in an institutional care facility (eg, nursing home, skilled care center)
  - Body Mass Index <20 kg/m^2
  - Grip strength <16 kg
  - Katz Index score ≤4
  - Albumin <3.5 g/dL

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