Current Status of TAVR in US and Future Prospects; Update on the PARTNER Trials; US TVT Registry

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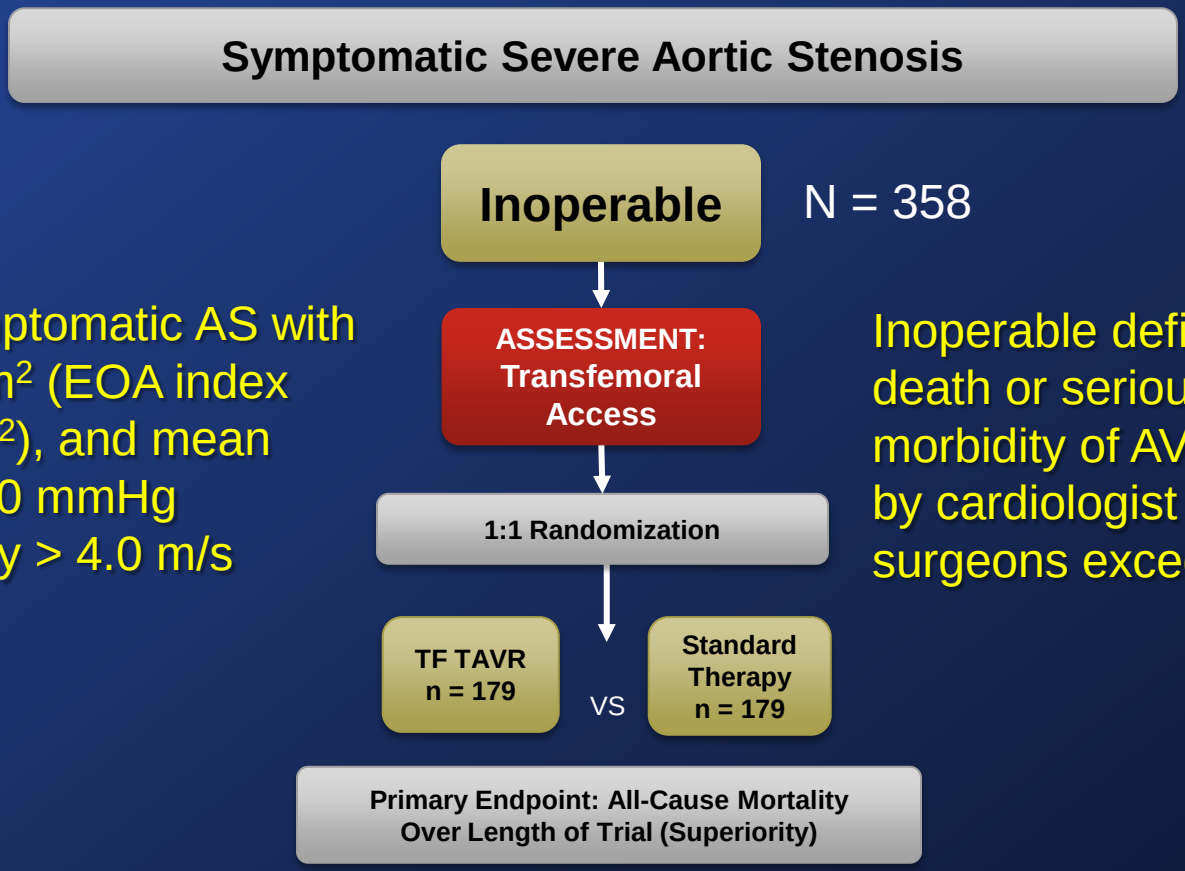
Conflict of Interest

- Member of Executive Committee of PARTNER Trial
- Sponsor- Edwards Lifesciences
- Uncompensated; travel expenses paid for committee meetings

PARTNER Pivotal TAVR Trials

- PARTNER I
  - Cohort A- High Surgical Risk
  - Cohort B – Inoperable
- PARTNER II
  - 2A- Intermediate Risk
  - Sapien 3- Inoperable, High Risk, Intermediate Risk

PARTNER Study Design

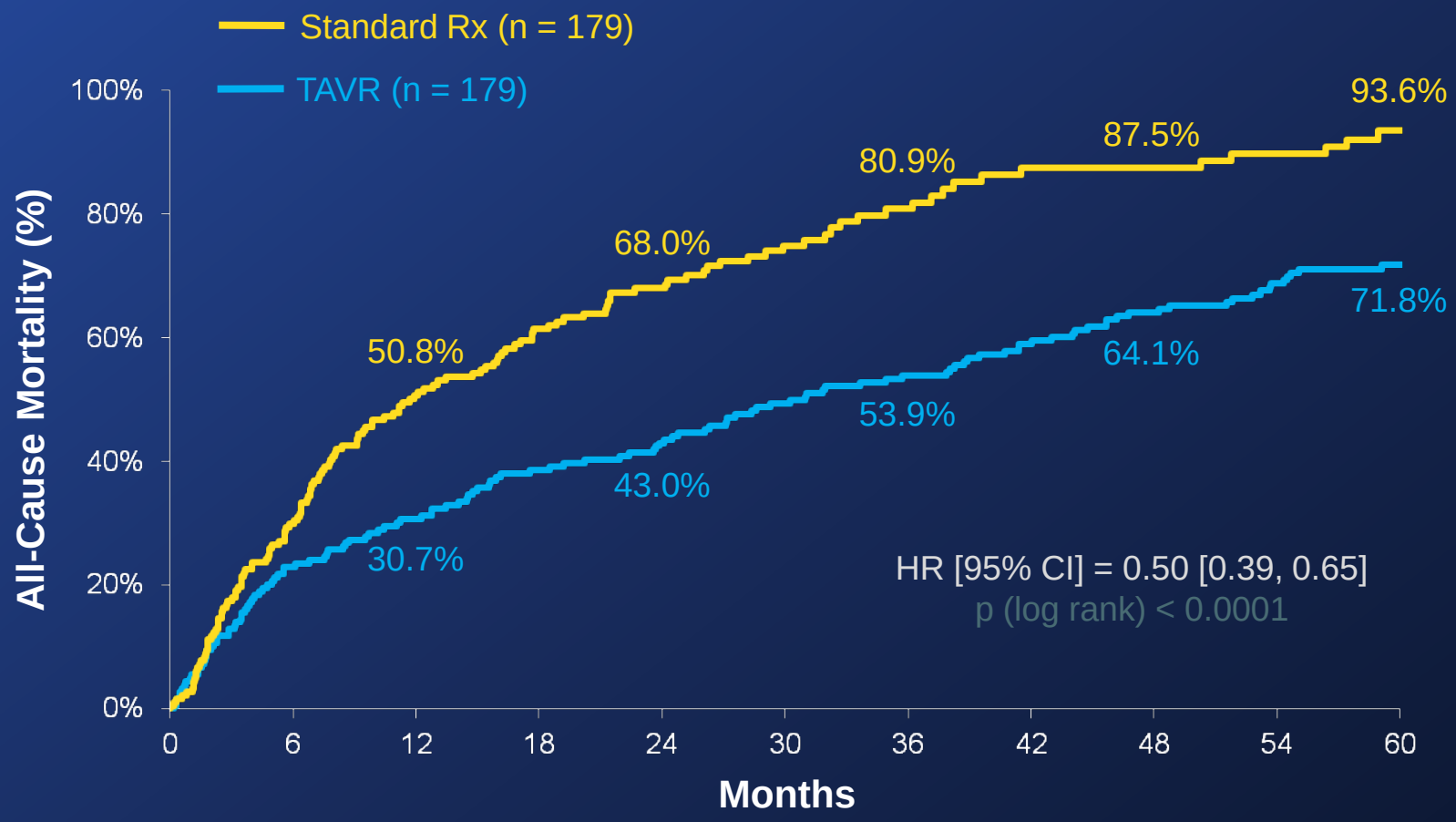


Severe Symptomatic AS with AVA< 0.8 cm^2 (EOA index < 0.5 cm^2/m^2), and mean gradient > 40 mmHg or jet velocity > 4.0 m/s

Inoperable defined as risk of death or serious irreversible morbidity of AVR as assessed by cardiologist and two surgeons exceeding 50%.

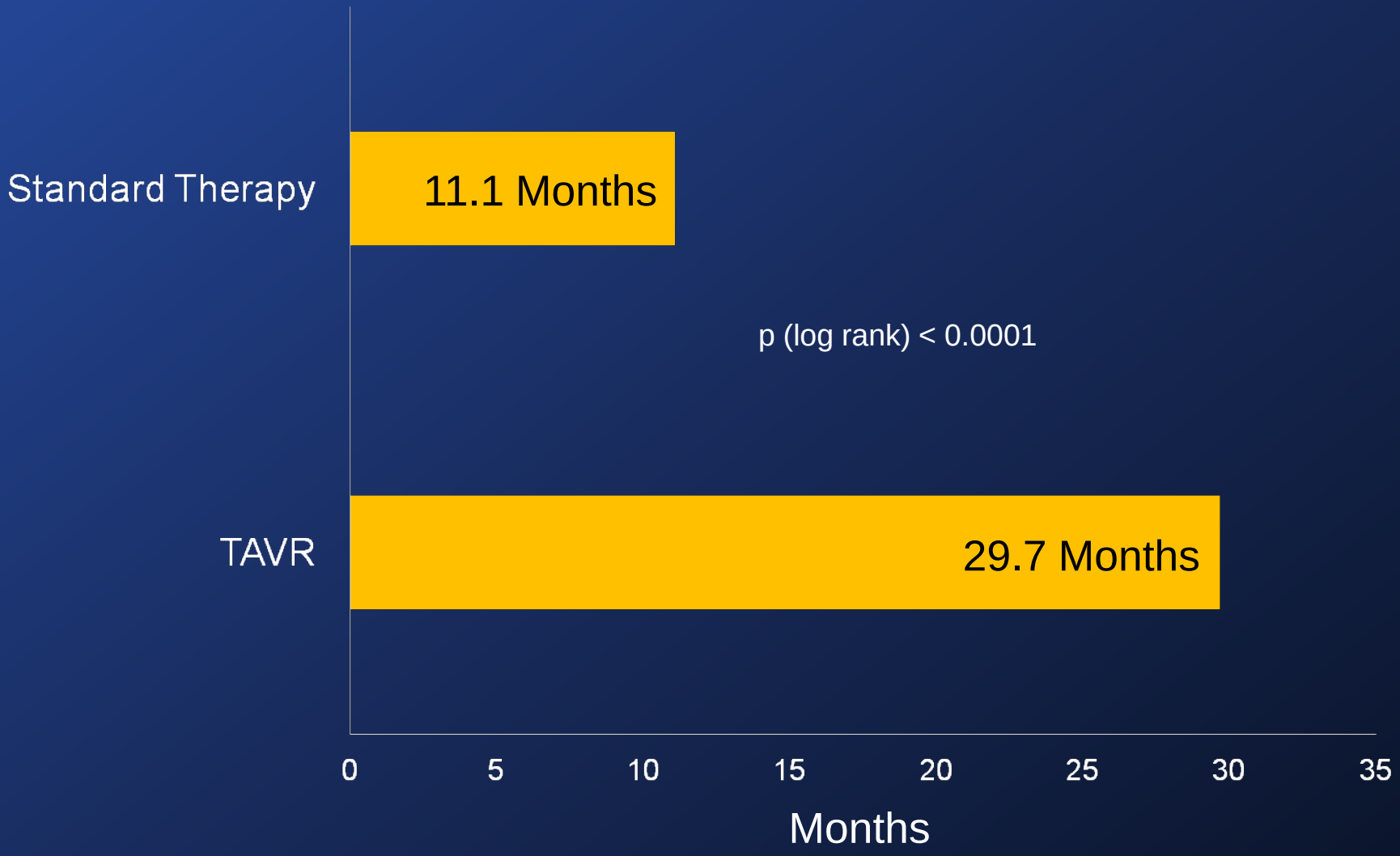
- *Primary endpoint evaluated when all patients reached one year follow-up.*
- *After primary endpoint analysis reached, patients were allowed to cross-over to TAVR.*

All-Cause Mortality (ITT)
Crossover Patients Censored at Crossover

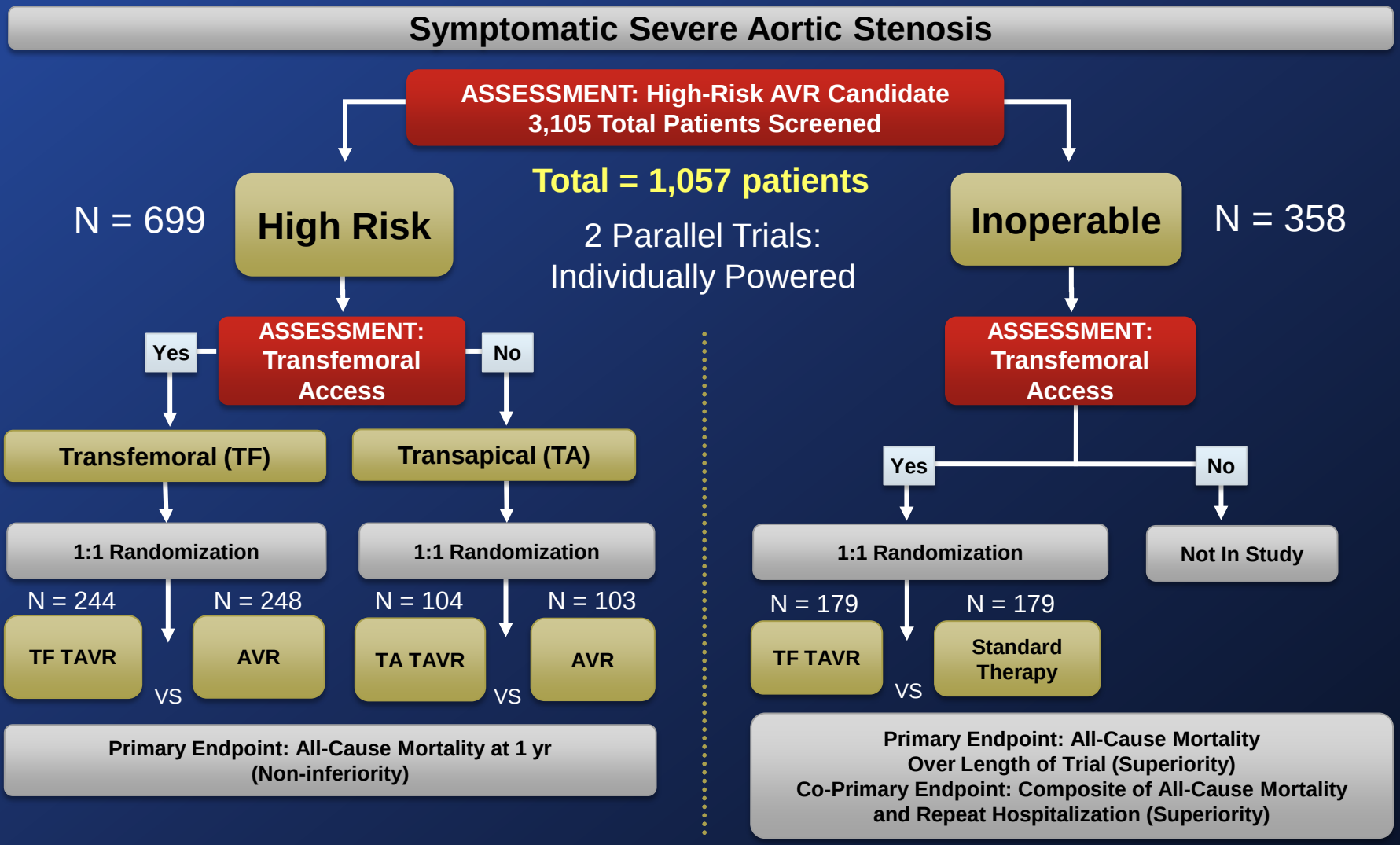


** In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.*

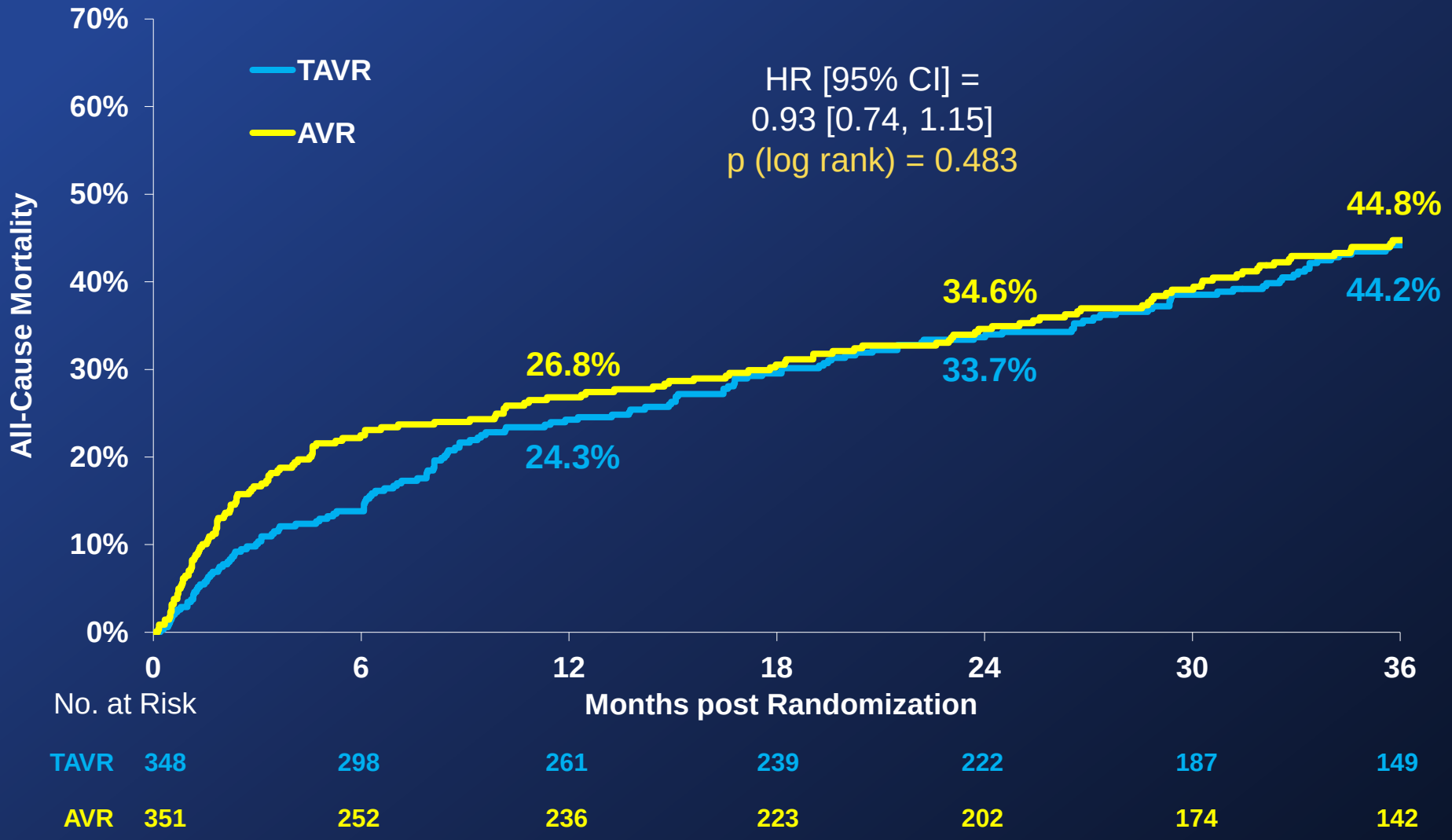
Median Survival



PARTNER Study Design



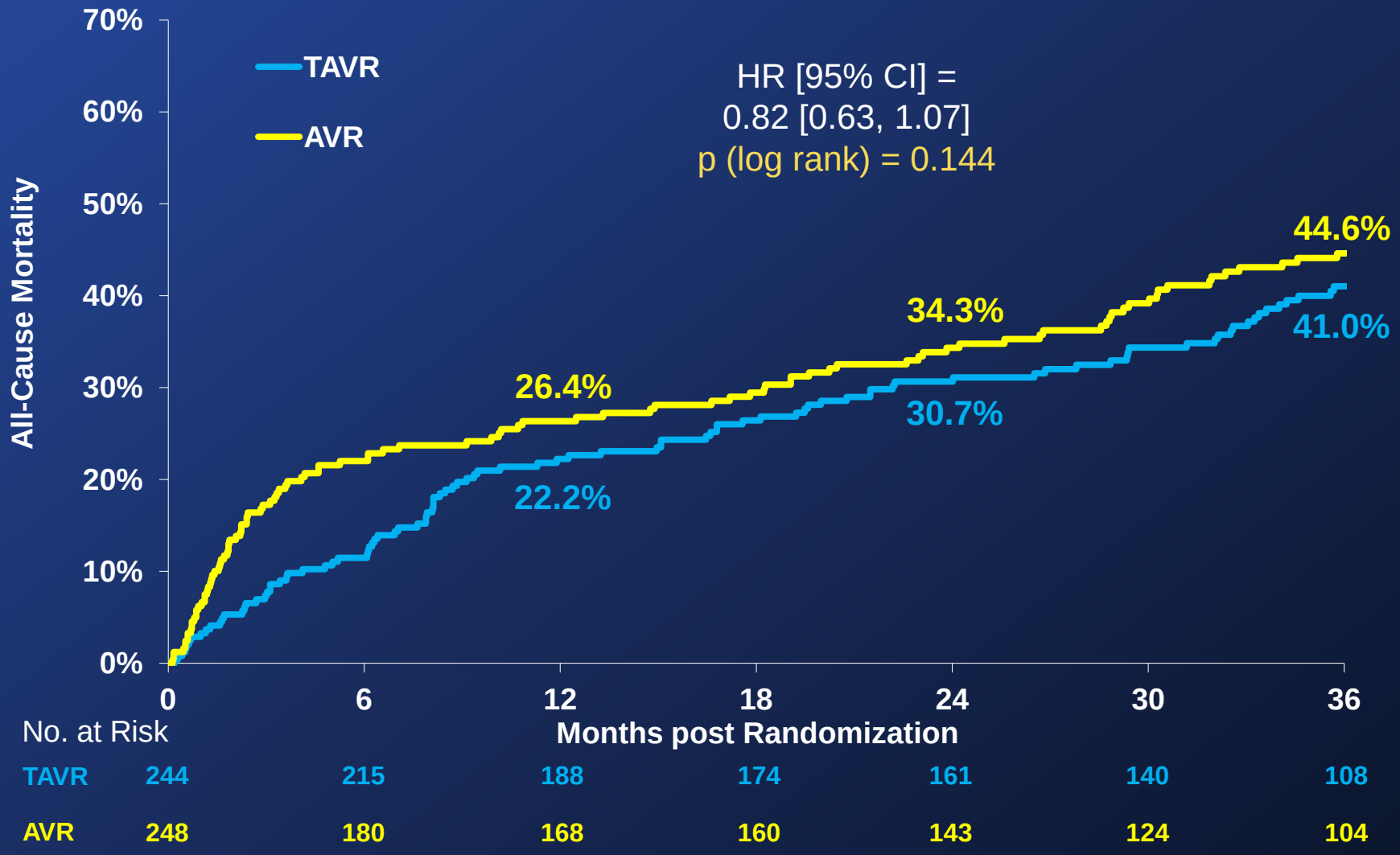
All-Cause Mortality (ITT)



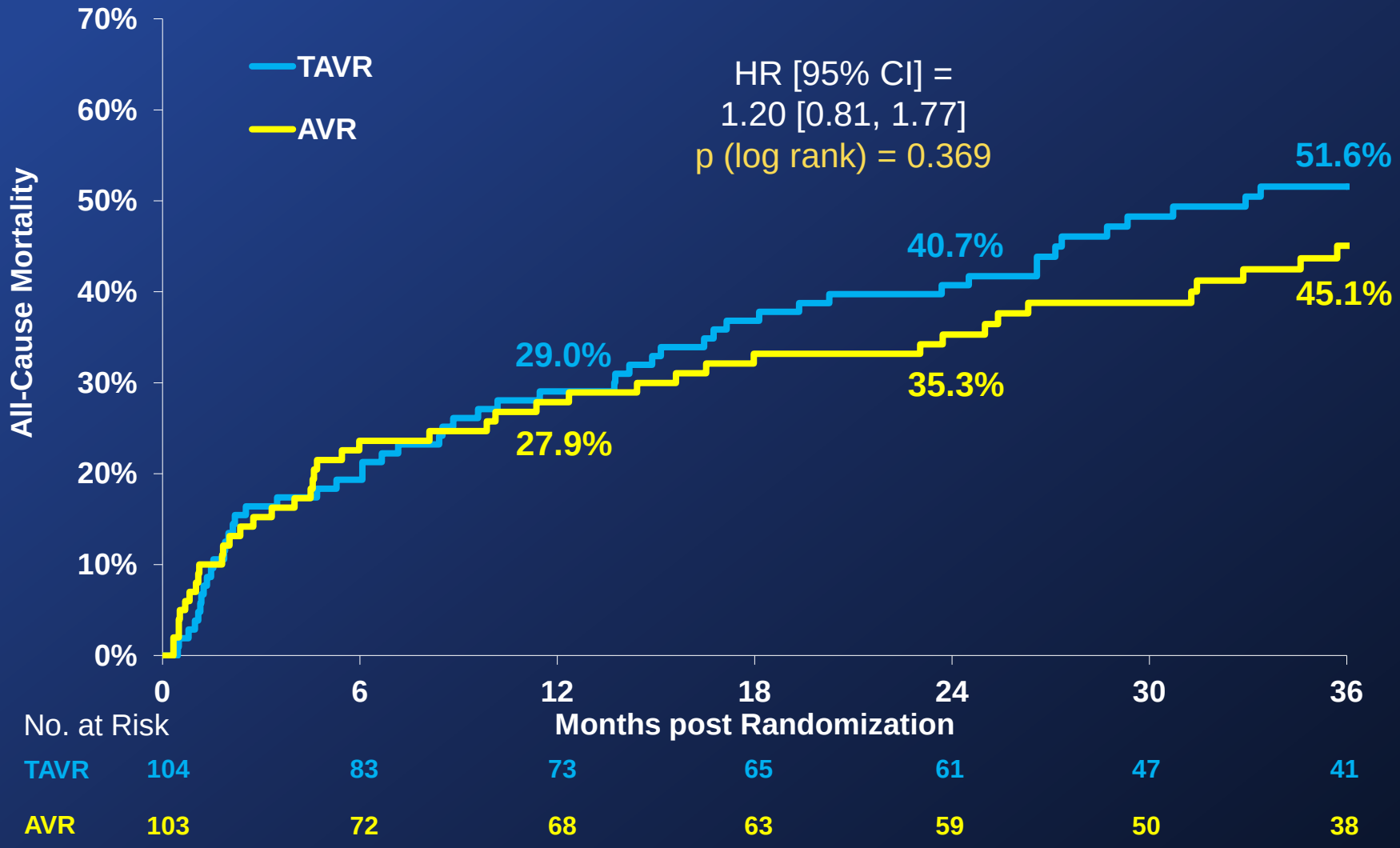
No. at Risk

TAVR	348	298	261	239	222	187	149
AVR	351	252	236	223	202	174	142

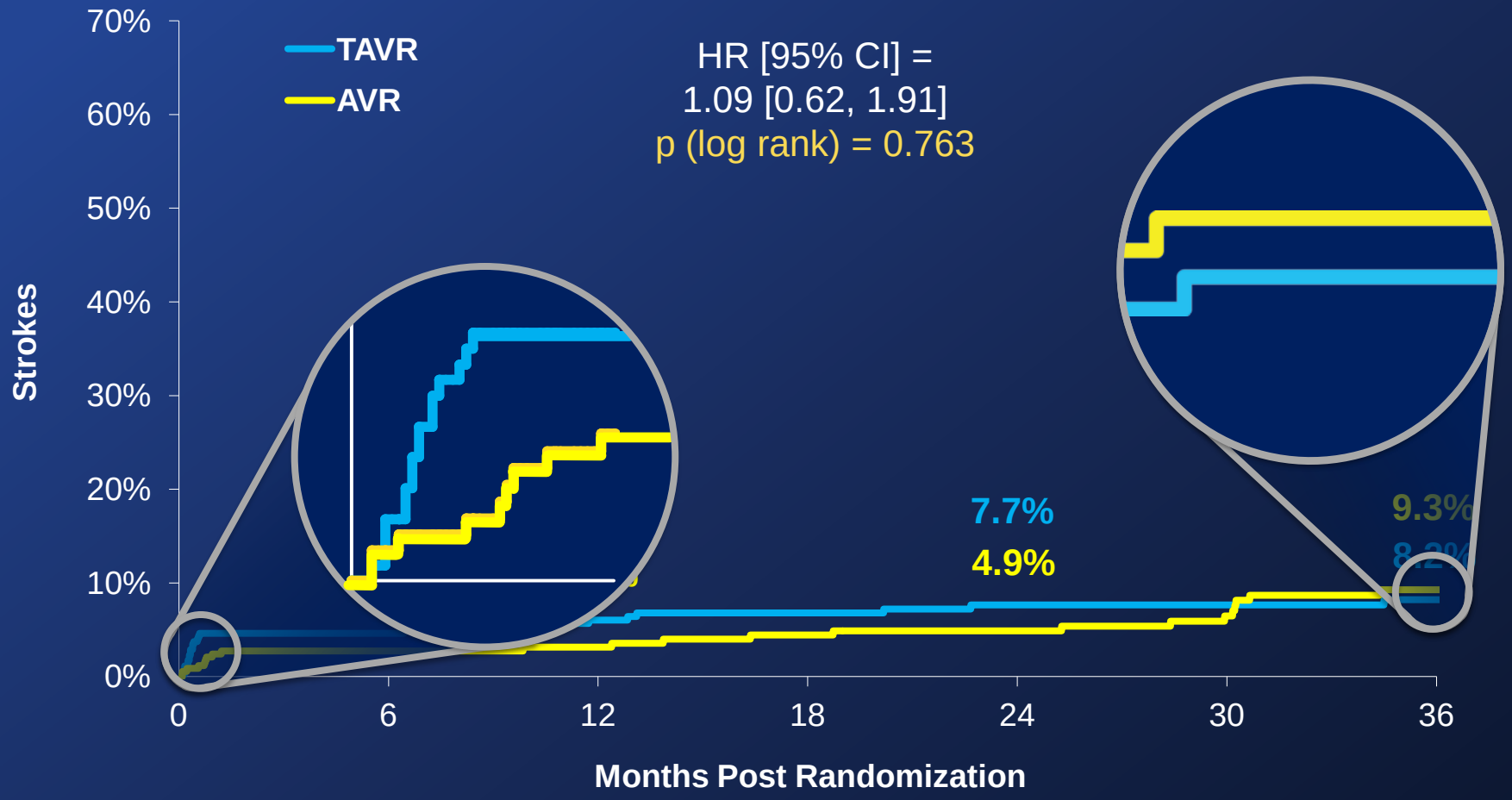
All-Cause Mortality (ITT)
Transfemoral



All-Cause Mortality (ITT)
Transapical



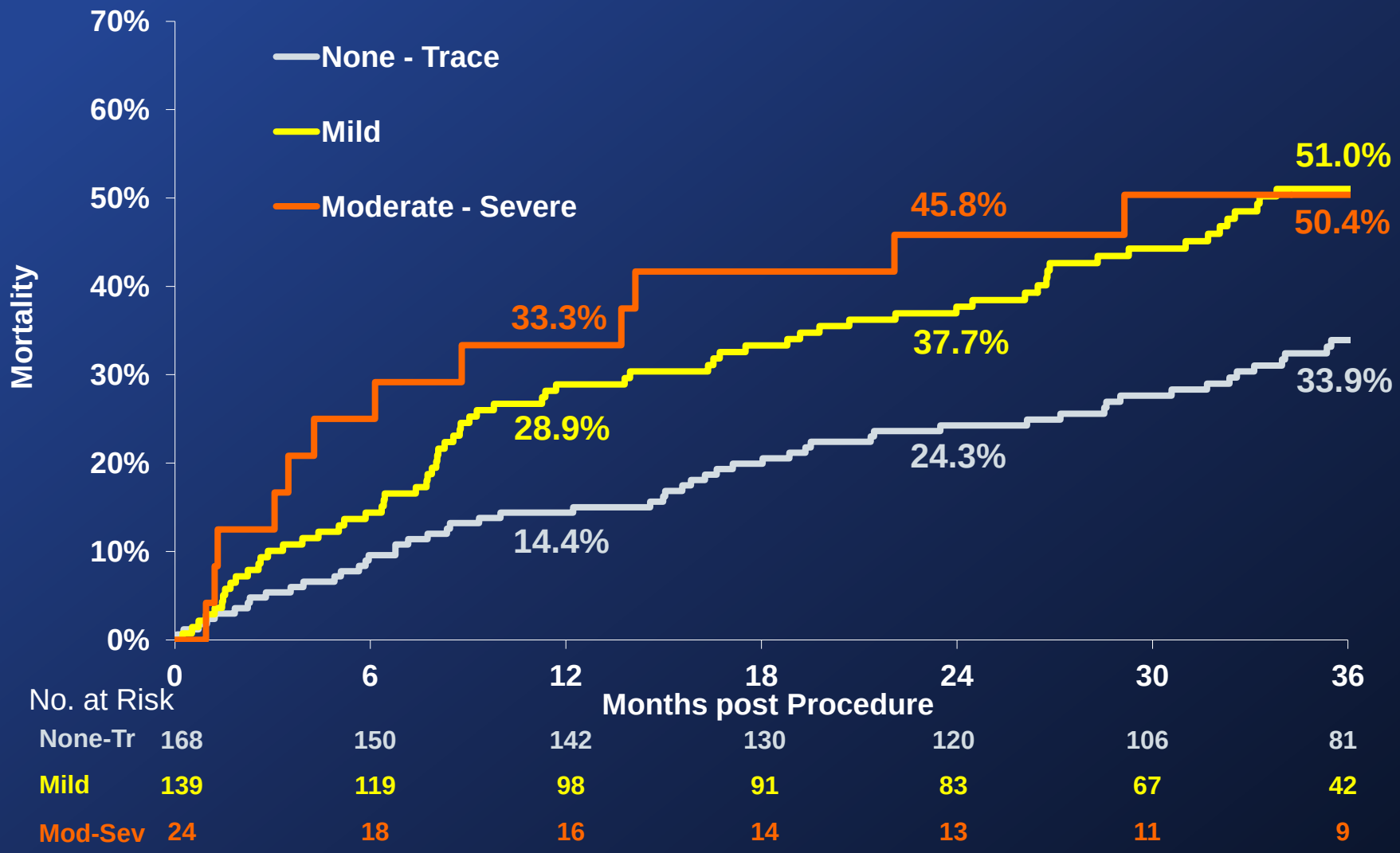
Strokes (ITT)



No. at Risk

TAVR	348	287	250	228	211	176	139
AVR	351	246	230	217	197	169	139

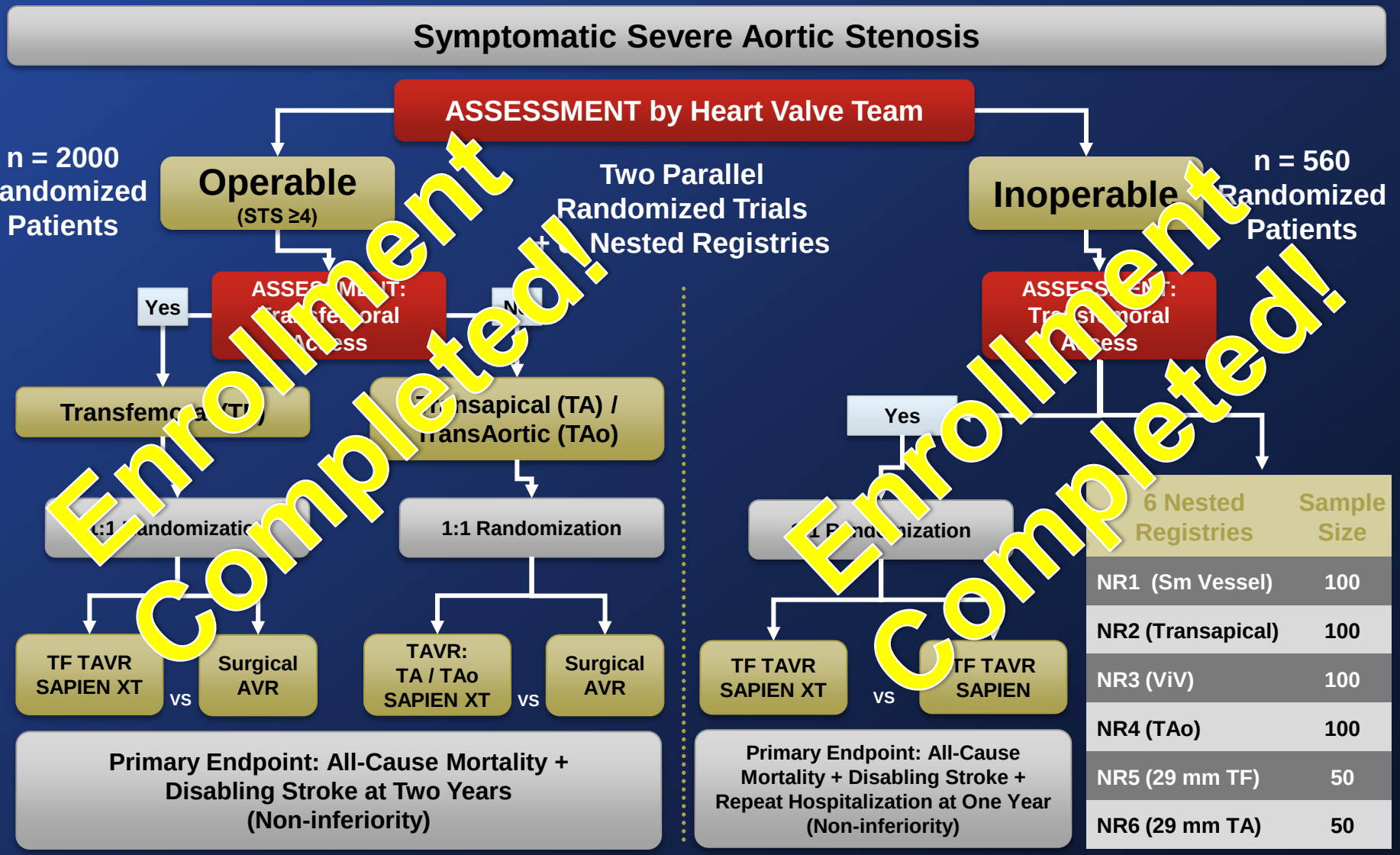
Impact of PVL on Mortality (AT)
TAVR Patients



No. at Risk

None-Tr	168	150	142	130	120	106	81
Mild	139	119	98	91	83	67	42
Mod-Sev	24	18	16	14	13	11	9

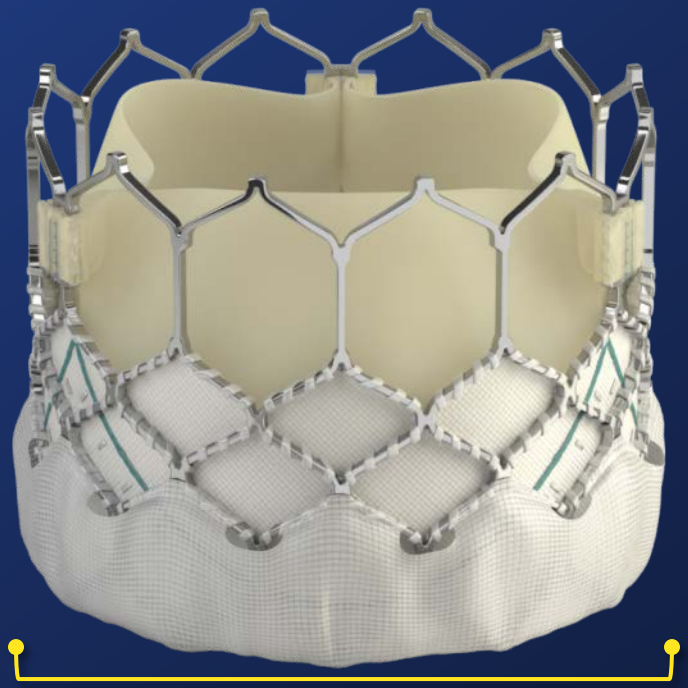
The PARTNER II Trial
Study Design



6 Nested Registries	Sample Size
NR1 (Sm Vessel)	100
NR2 (Transapical)	100
NR3 (ViV)	100
NR4 (TAo)	100
NR5 (29 mm TF)	50
NR6 (29 mm TA)	50

Edwards SAPIEN 3 THV

SAPIEN 3 Valve Size	23 mm	26 mm	29 mm
Edwards eSheath Introducer Set	14F	14F	16F
Minimum Access Vessel Diameter	5.5 mm	5.5 mm	6.0 mm



Outer skirt

- Designed to minimize paravalvular leak

* No clinical data are available which evaluate the long-term impact of the Carpentier-Edwards ThermaFix process in patients

30-Day Outcomes From

John Webb, MD

On Behalf of the SAPIEN 3 Investigators
University of British Columbia
Vancouver, Canada

THE PARTNER TRIAL

Edwards SAPIEN 3 THV

	The SAPIEN 3 Trial
Study Design	Prospective, multicenter, non-randomized study
Number of Patients	150 (TF [transfemoral] = 96, TAA [transapical / transaortic] = 54)
Patient Selection	**50 high-risk patients & 100 high-risk or intermediate-risk patients** • **High-risk:** STS score ≥ 8 or Logistic EuroSCORE ≥ 15 • **Intermediate-risk:** STS score ≥ 4 to < 8 or Logistic EuroSCORE ≥ 10 to < 15
Enrollment Period	January 2013 to November 2013
Study Centers	16 sites in Europe and Canada
Access Approach	Transfemoral, transapical, or transaortic access, as determined by the Heart Team

Edwards SAPIEN 3 THV

THE PARTNER TRIAL EMORY

Baseline Characteristics (%)	TF PATIENTS (N = 96)	TAA PATIENTS (N = 54)	P-VALUE
STS PROM Score	7.5 ± 4.26	7.3 ± 4.94	0.813
Logistic EuroSCORE (%)	19.8 ± 10.9	24.9 ± 14.0	0.022
Peripheral Vascular Disease	16.7	38.9	0.003
Previous Myocardial Infarction	11.5	27.8	0.014
Previous CABG	14.6	27.8	0.056
Atrial Fibrillation	22.9	35.8	0.125
Previous Aortic Valvuloplasty	10.4	3.7	0.213
Previous Pacemaker Implantation	13.5	16.7	0.635
Carotid Disease	25.0	25.9	1.000
Porcelain Aorta	1.0	1.9	1.000
Prior Stroke	7.3	7.4	1.000

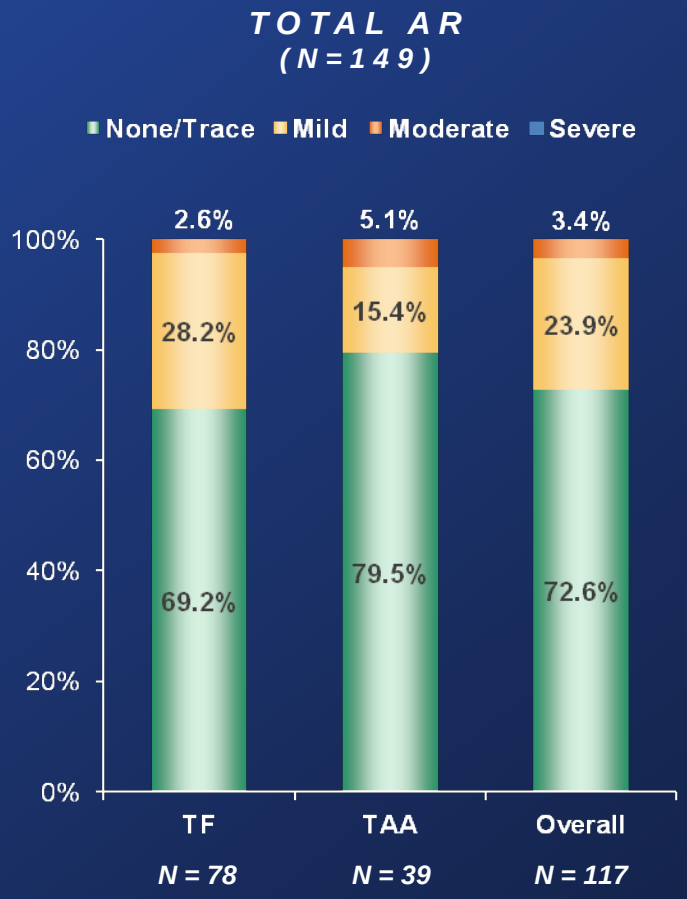
Edwards SAPIEN 3 THV

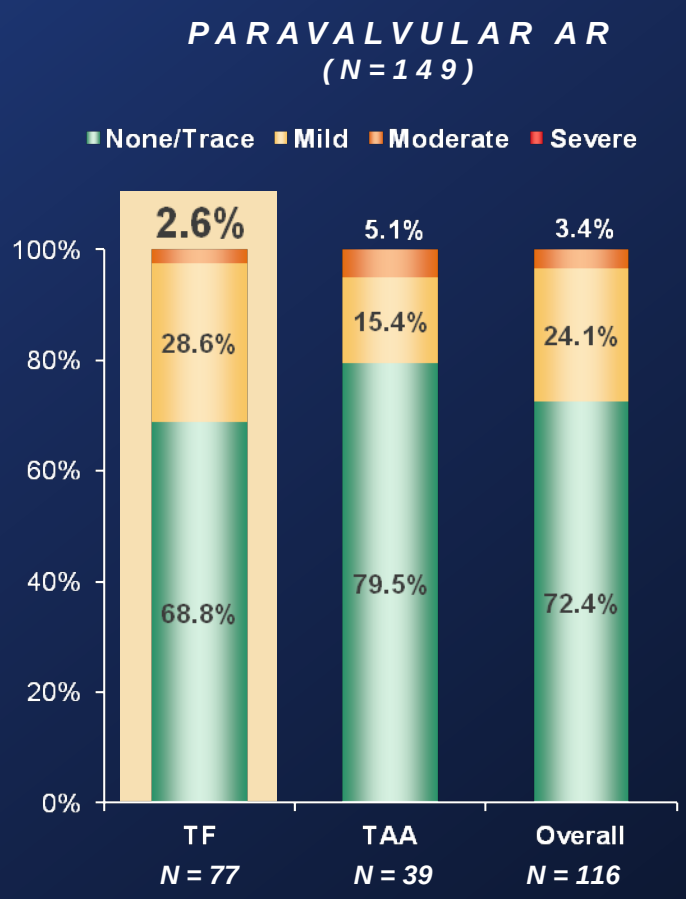
Clinical Outcome	EVENT RATE IN THE AT POPULATION # PATIENTS (KM %)		
	TF (N = 96)	TAA (N = 54)	Overall (N = 150)
All-Cause Mortality	2 (2.1%)	6 (11.1%)	8 (5.3%)
Cardiac Mortality	2 (2.1%)	5 (9.3%)	7 (4.7%)
All-Stroke*	1 (1.0%)	3 (5.6%)	4 (2.7%)
Disabling Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)
Major Vascular Complication	5 (5.2%)	4 (7.4%)	9 (6.0%)
Major Bleeding	19 (19.8%)	11 (20.4%)	30 (20.0%)
Life-Threatening Bleeding	2 (2.1%)	3 (5.6%)	5 (3.3%)
Rehospitalization†	0 (0.0%)	0 (0.0%)	0 (0.0%)

Primary Endpoint	EVENT RATE IN THE VI POPULATION # PATIENTS (KM %)		
	TF (N = 95)	TAA (N = 54)	Overall (N = 149)
All-Cause Mortality	1 (1.1%)	6 (11.1%)	7 (4.7%)

VI, valve implant = all enrolled patients who received a SAPIEN 3 implant, and retain the valve upon leaving the cath lab
** Severity of the one TF stroke unknown.*
† Rehospitalization for valve-related symptom or worsening of congestive heart failure.

Edwards SAPIEN 3 THV





The Edwards SAPIEN 3 transcatheter heart valve is an investigational device. Limited by Federal (United States) Law to investigational use only

What We Have Learned

- Clear mortality benefit with TAVR in inoperable/extreme risk AS patients
- Outcomes comparable to SAVR in high risk patients
- Improved recent outcomes due to:
  - Newer generation devices
  - Surmounted learning curve
  - Lower risk patients treated
  - Improved patient selection (less Cohort C patients)
- Paravalvular leaks appears to be decreasing

Stay Tuned !- ACC LBCT

- PARTNER 1A -5 Year
- COREVALVE- High Risk 2 Year
- PARTNER 2 - Sapien 3 - Inoperable, High Risk & Intermediate -30 day

How is TAVR Implemented in the U.S; Lessons from TVT Registry

Original Investigation

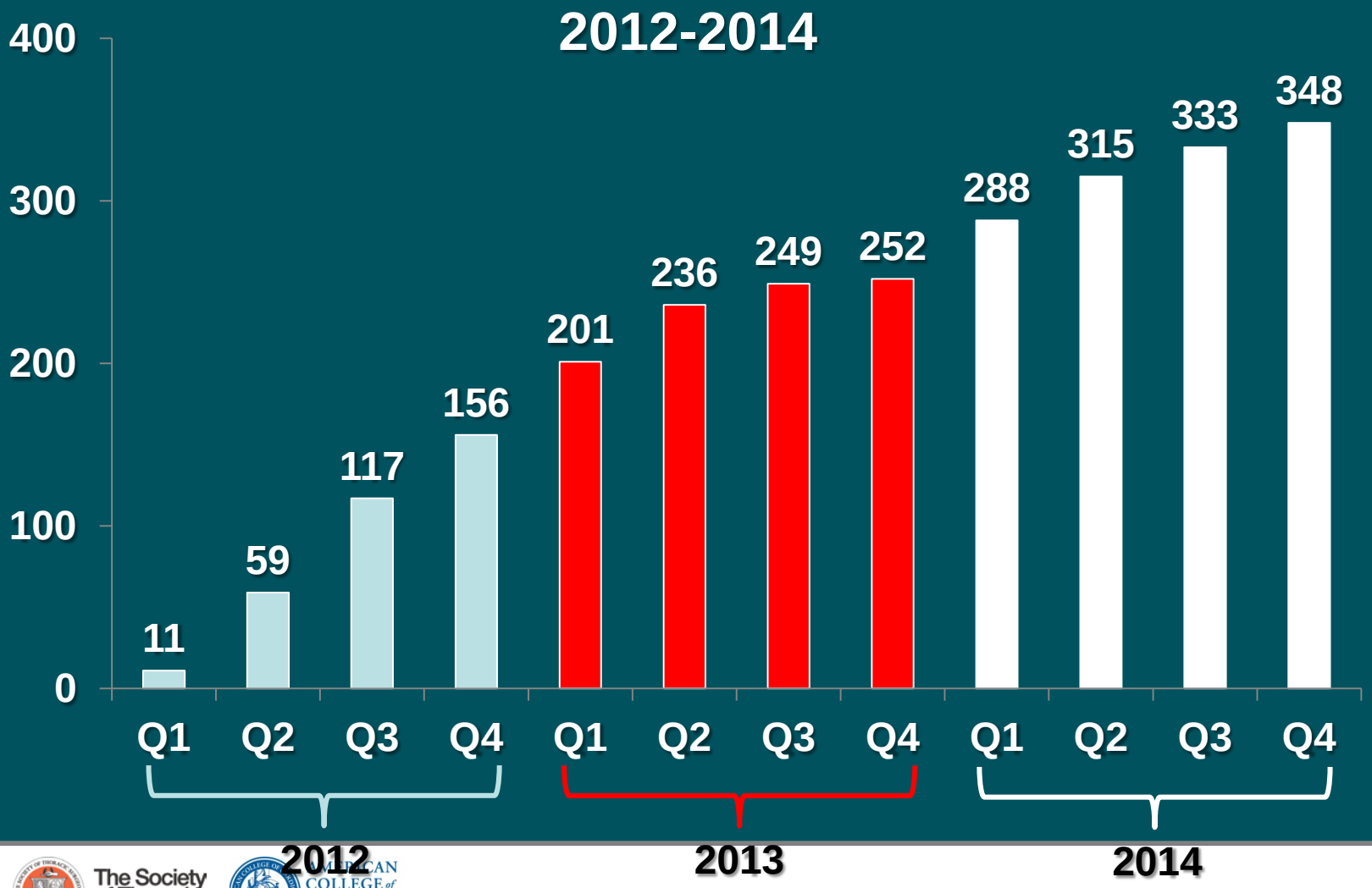
Outcomes Following Transcatheter Aortic Valve Replacement in the United States

Michael J. Mack, MD; J. Matthew Brennan, MD, MPH; Ralph Brindis, MD, MPH; John Carroll, MD; Fred Edwards, MD; Fred Grover, MD; David Shahian, MD; E. Murat Tuzcu, MD; Eric D. Peterson, MD, MPH; John S. Rumsfeld, MD, PhD; Kathleen Hewitt, MSN; Cynthia Shewan, PhD; Joan Michaels, RN; Barb Christensen, RN; Alexander Christian; Sean O'Brien, PhD; David Holmes, MD; for the STS/ACC TVT Registry

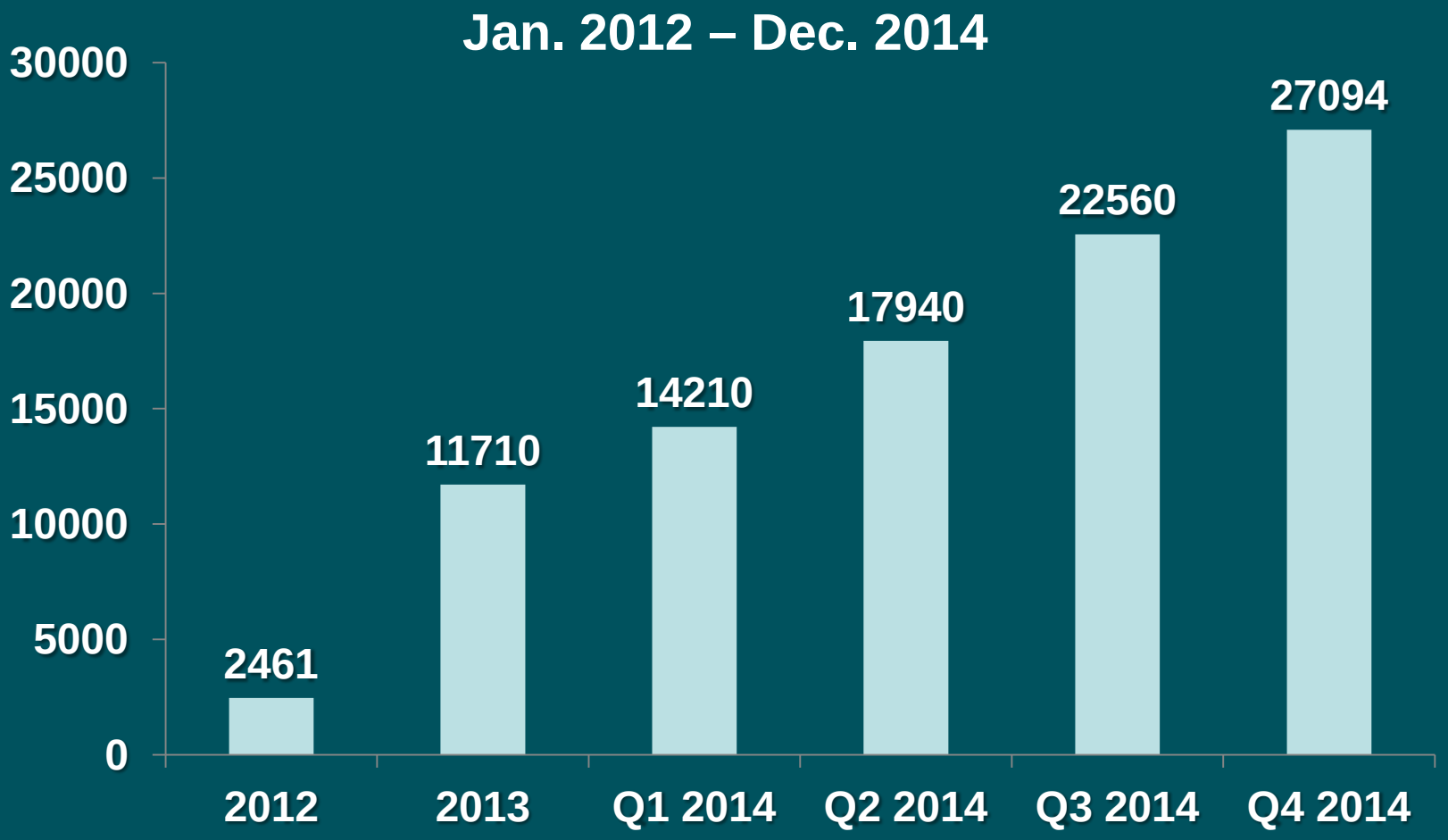
Table 4. 30-Day Clinical Outcomes[a]

Outcomes	Overall (n = 3528)	High Risk (n = 2834)		Inoperable (n = 694)	
		Trans-femoral (n = 1687)	Nontrans-femoral (n = 1147)	Trans-femoral (n = 489)	Nontrans-femoral (n = 205)
Death	243 (7.6)	77 (5.0)	112 (10.8)	30 (6.7)	24 (12.6)

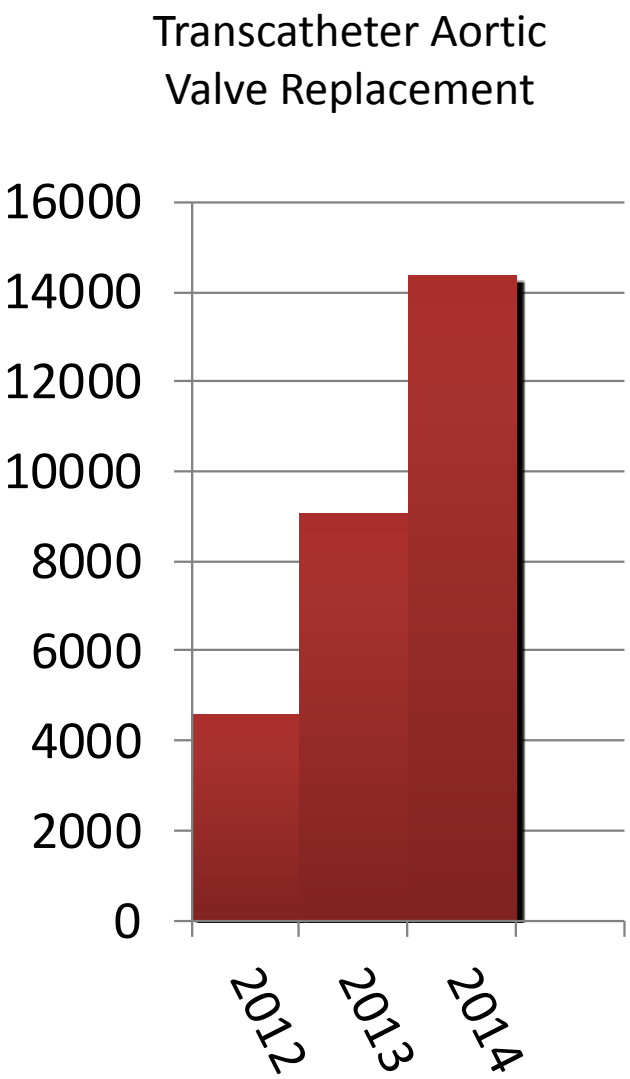
Cumulative Sites Enrolled in TVT Registry

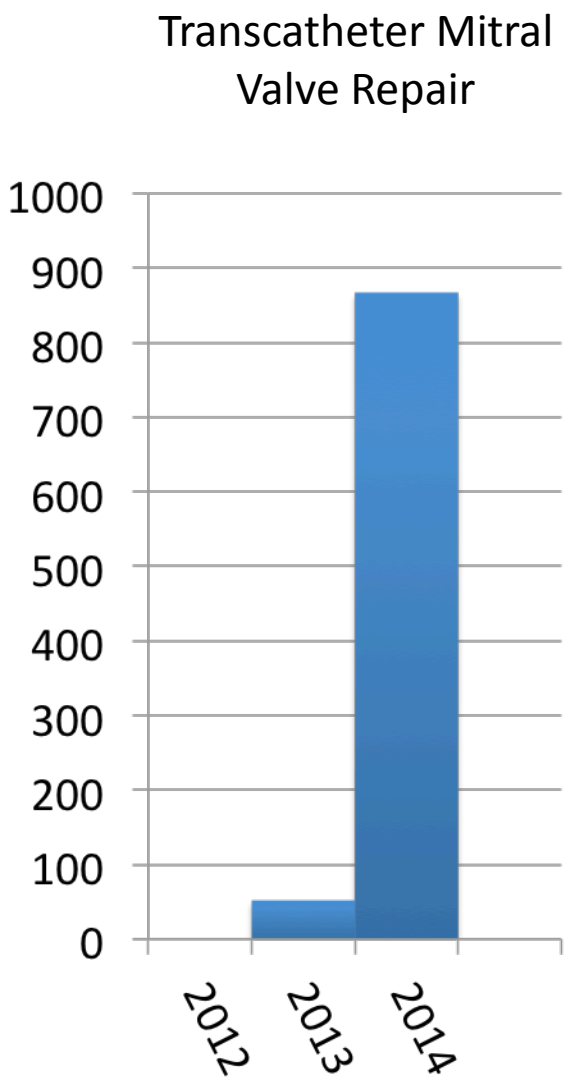


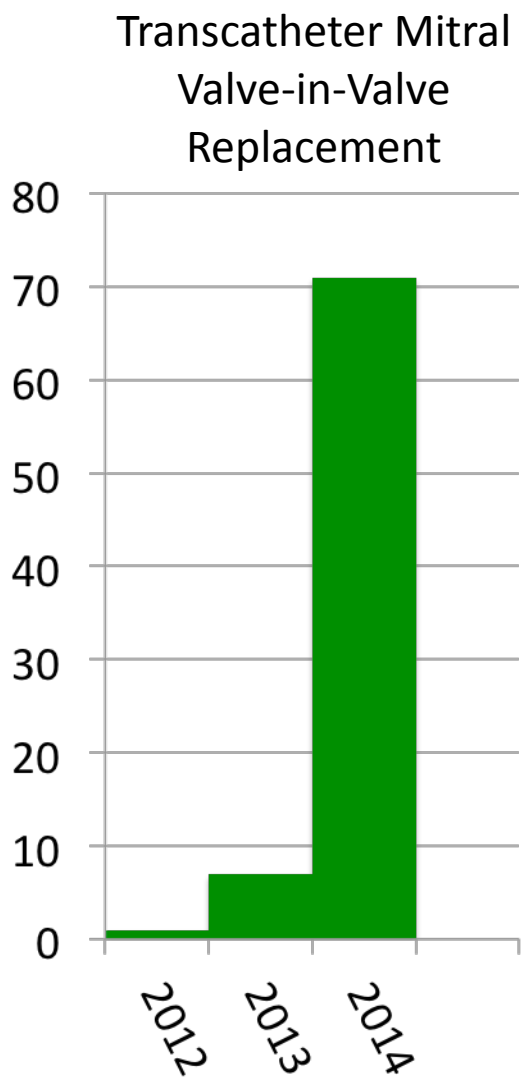
Cumulative TVT Records Submitted to TVT Registry



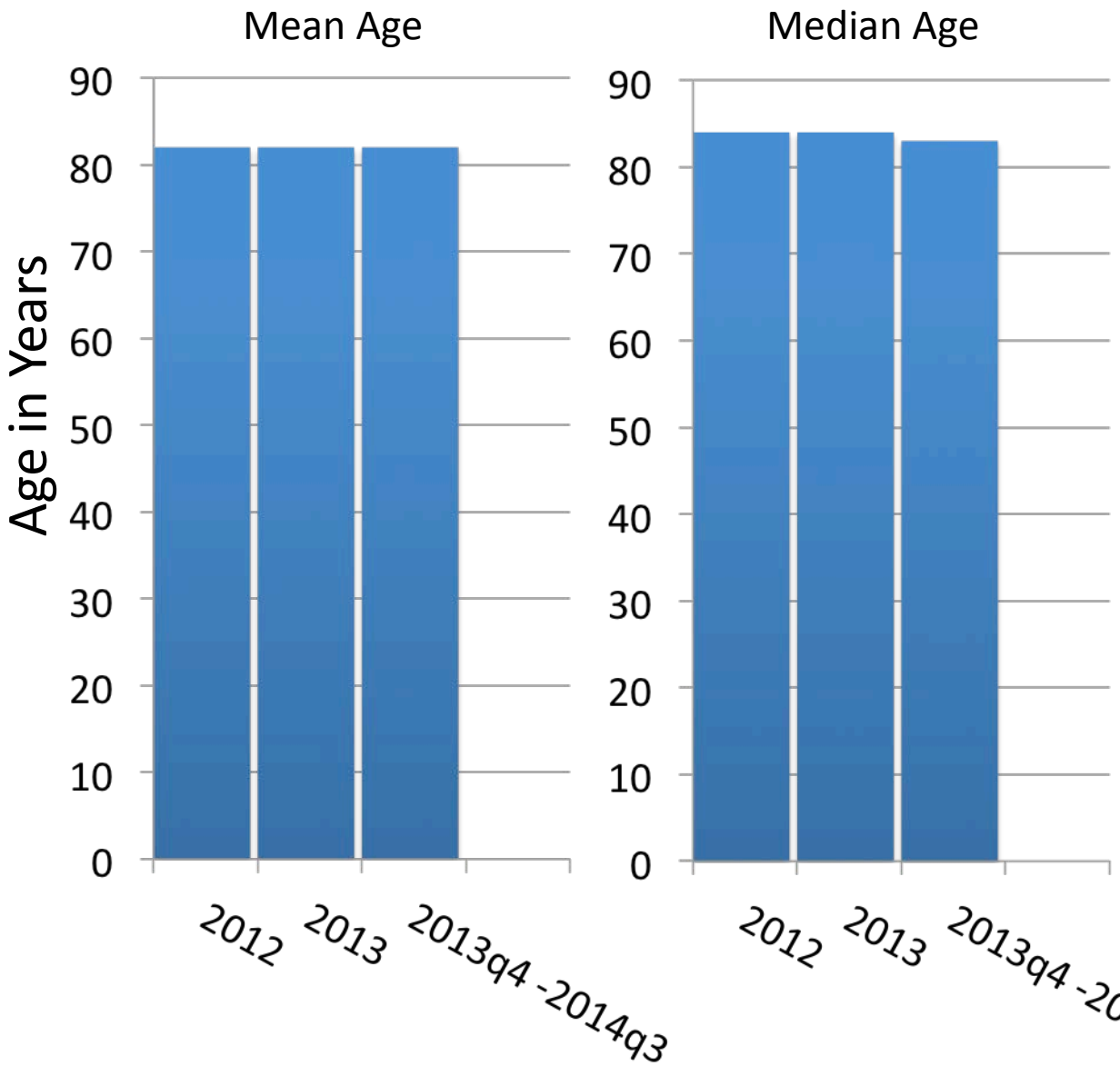
Yearly Registry Volume By Procedure Type





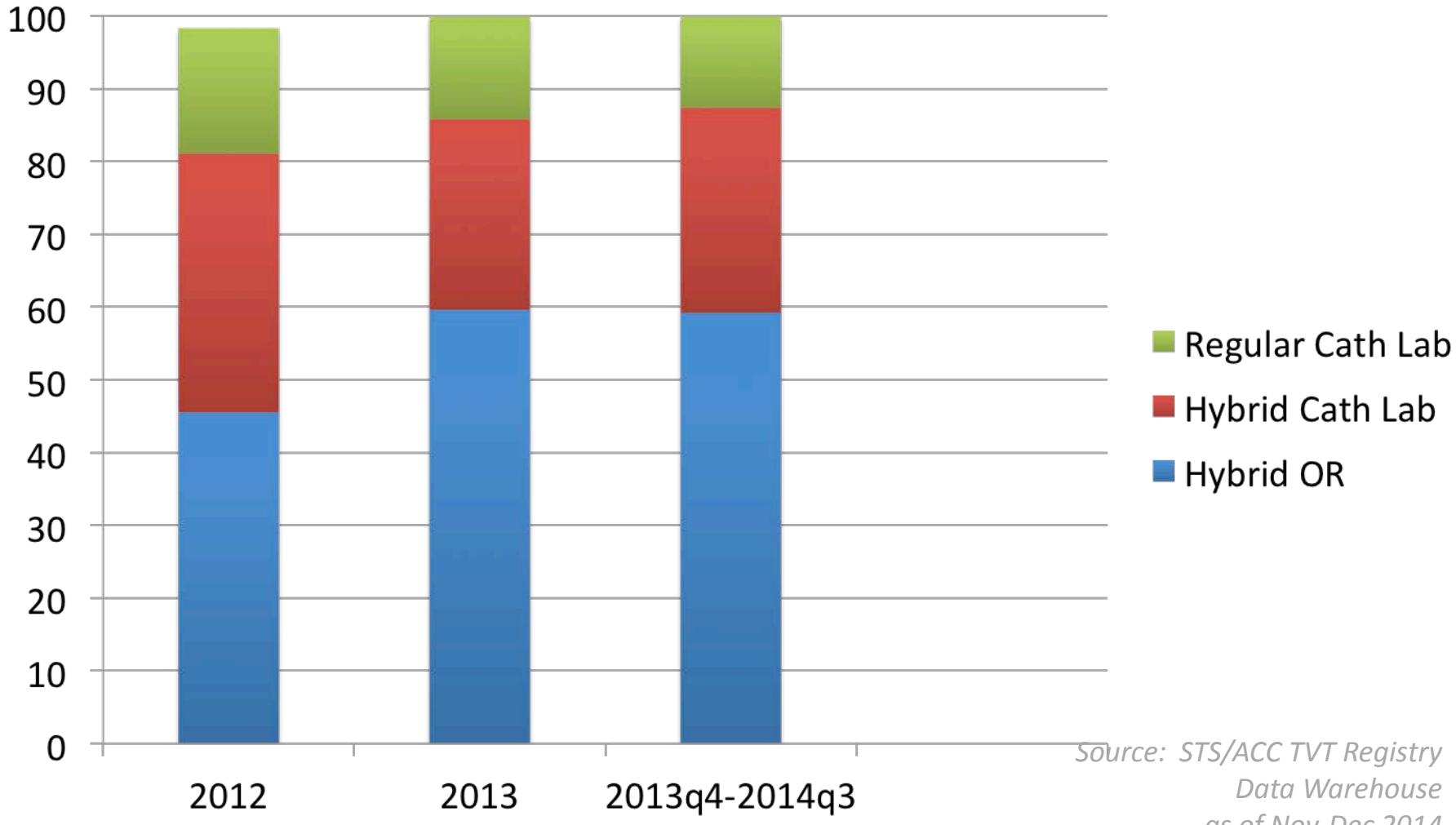


TAVR: Age of the Patients



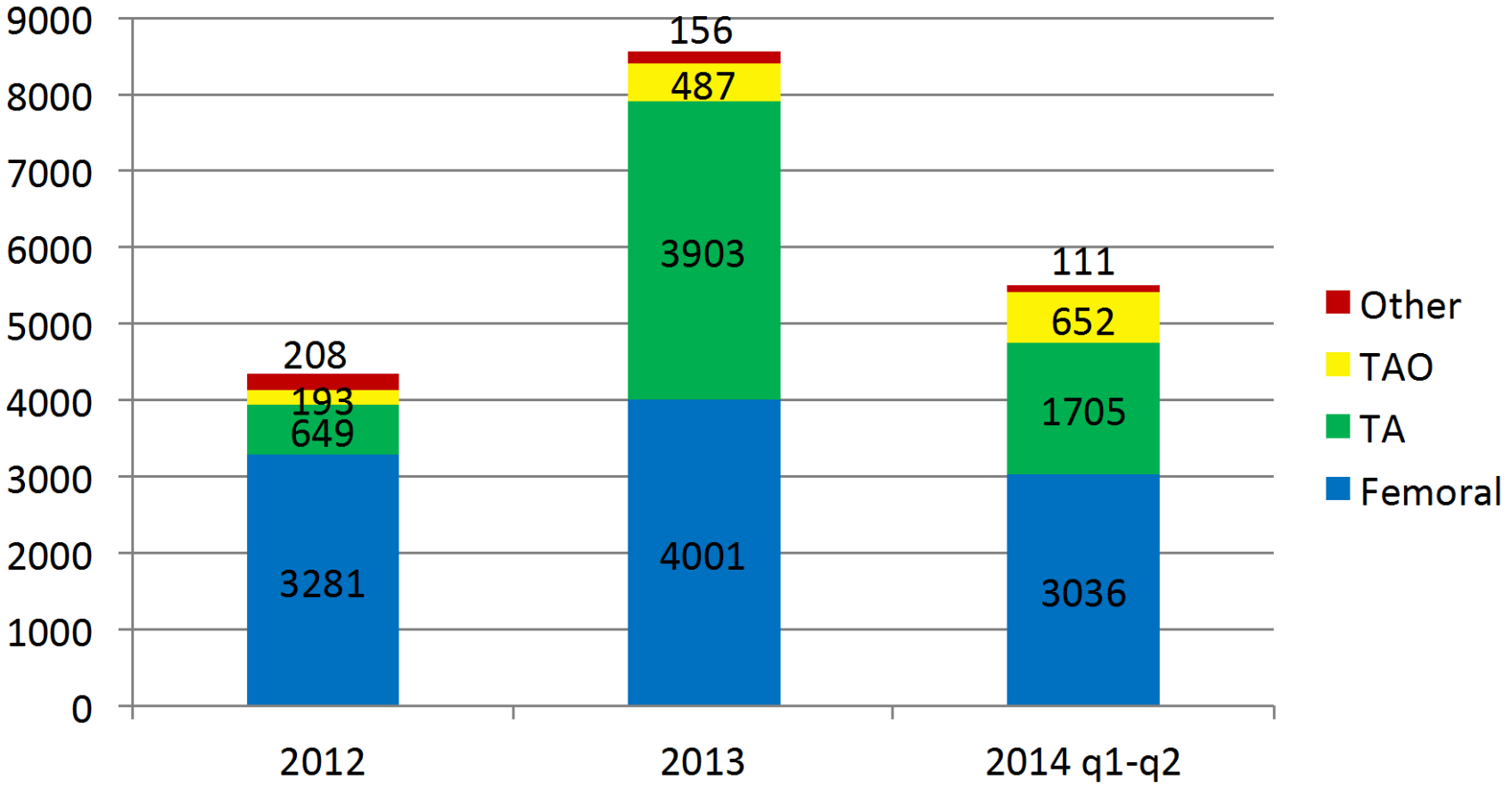
- *There Does Not Appear to Be Significant Age Creep in TAVR in the US*

TAVR – Where Performed



Source: STS/ACC TVT Registry Data Warehouse as of Nov-Dec 2014

Access Site



Source: STS/ACC TVT Registry (7/1/2012-6/30/2014)

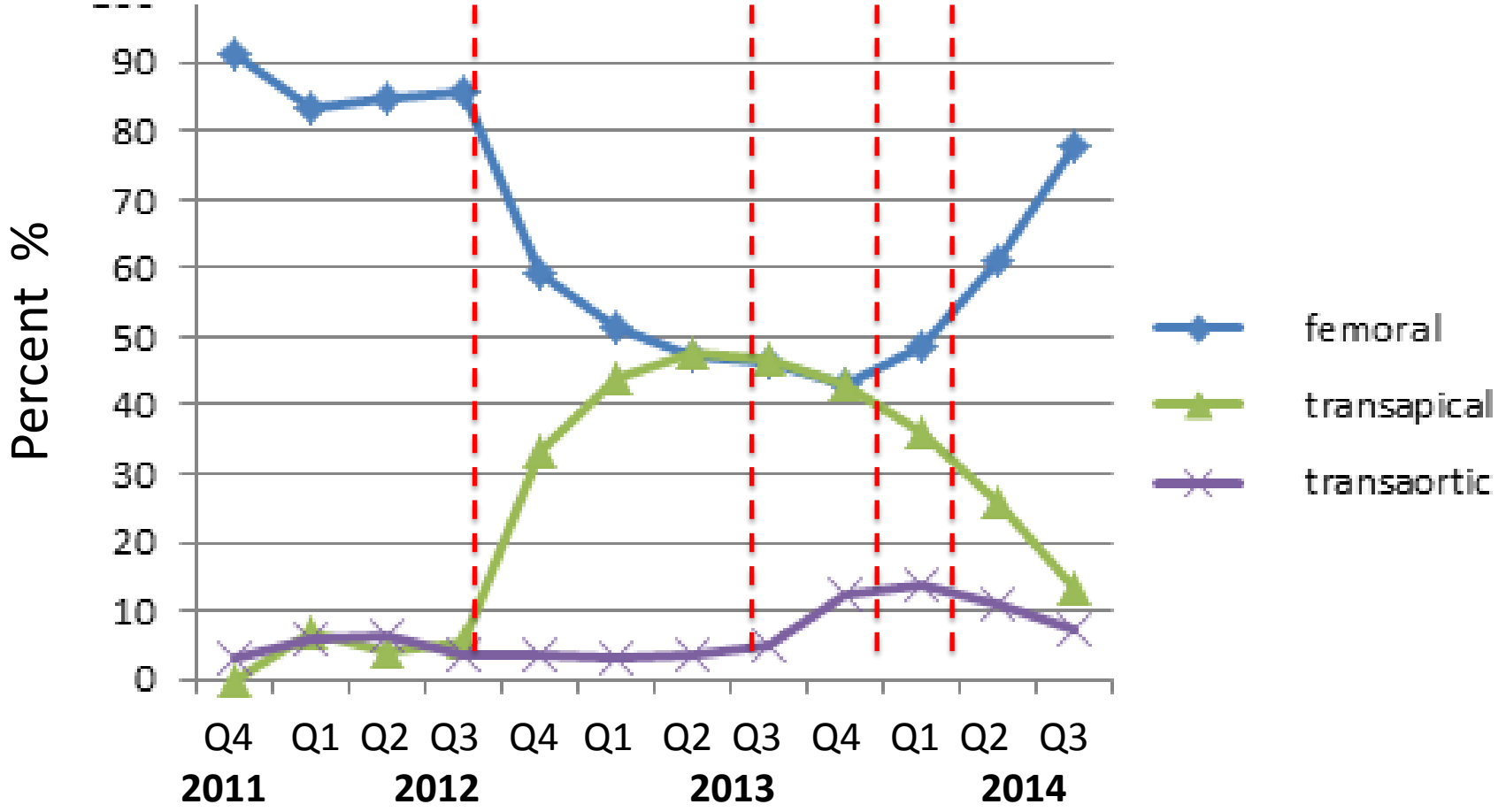
US Trends in Access & Impact of New Technologies

2012 October
FDA extends Sapien approval to high-risk patients using femoral or other access

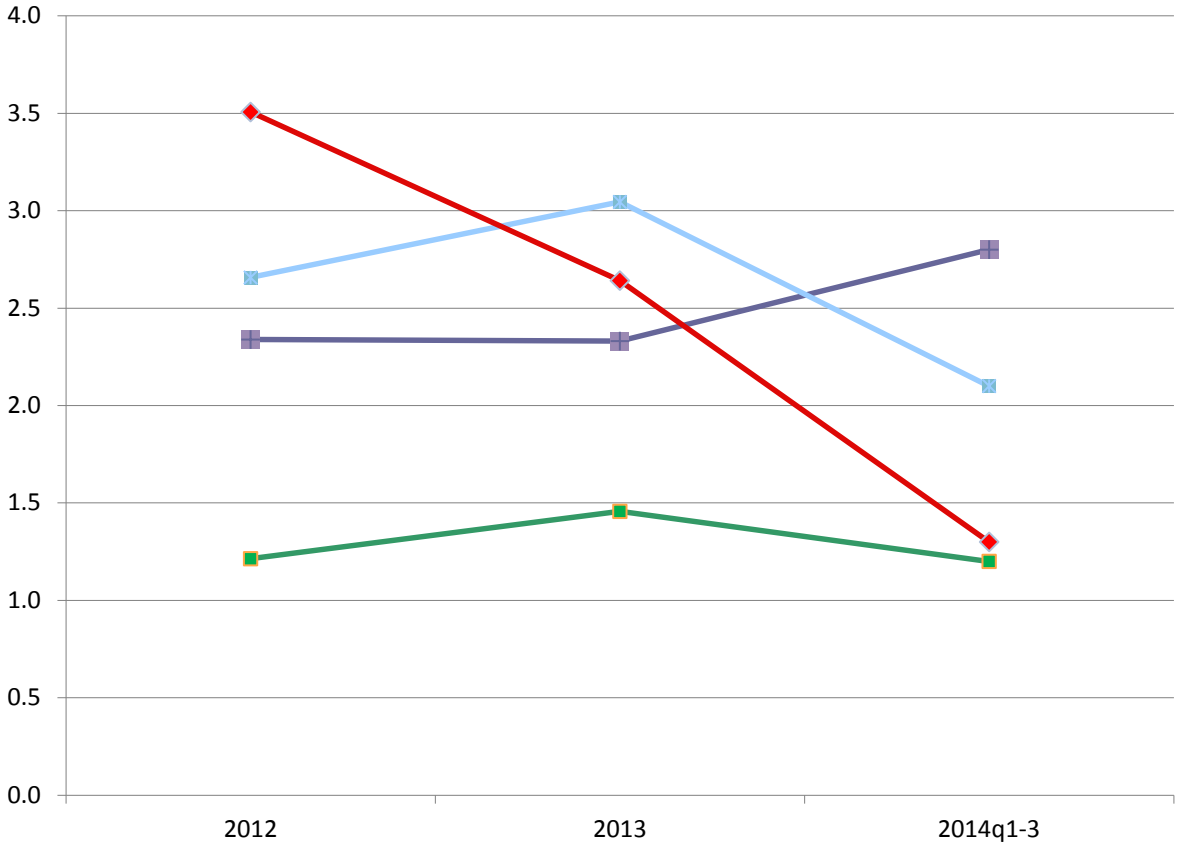
2013 September
FDA extends Sapien using registry data to inoperable patients for all vascular access

2014 January
FDA approves CoreValve for extreme-risk patients

2014 June
FDA extends CoreValve for high-risk patients and approves Sapien XT

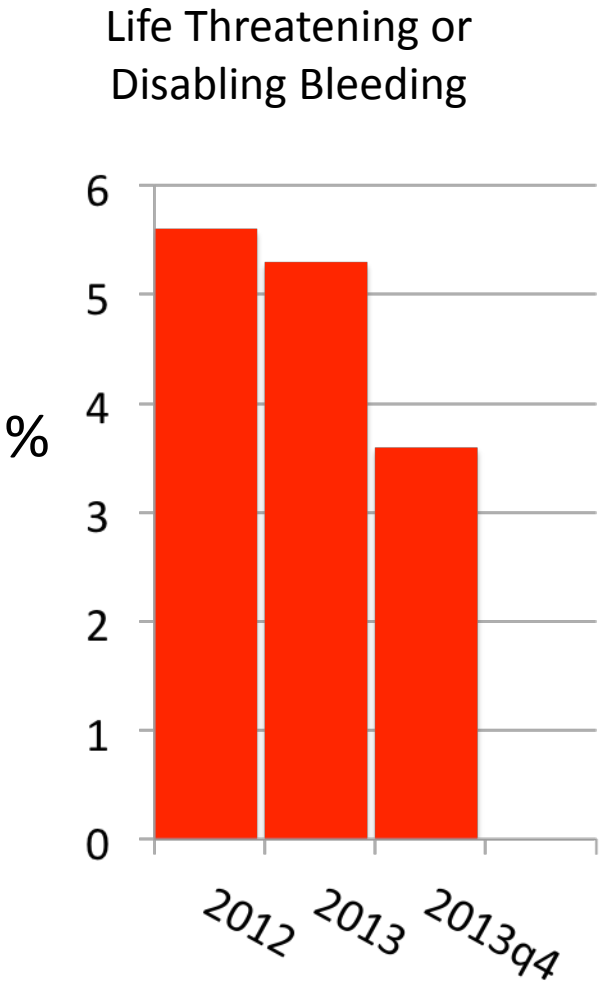


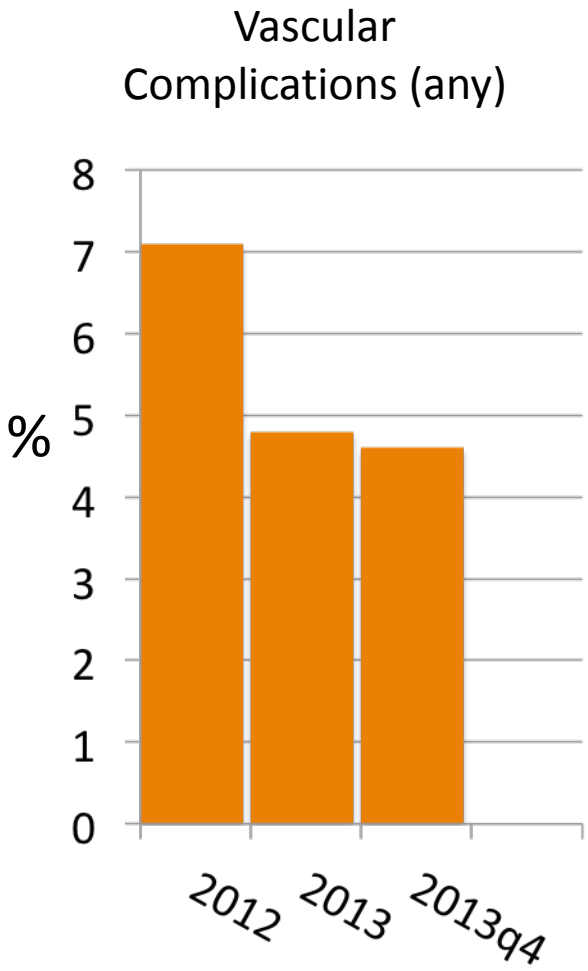
Procedure Outcomes



Source: STS/ACC TVT Registry Database
23,557 records from 2012q1-2014q3 as of 2-13-15

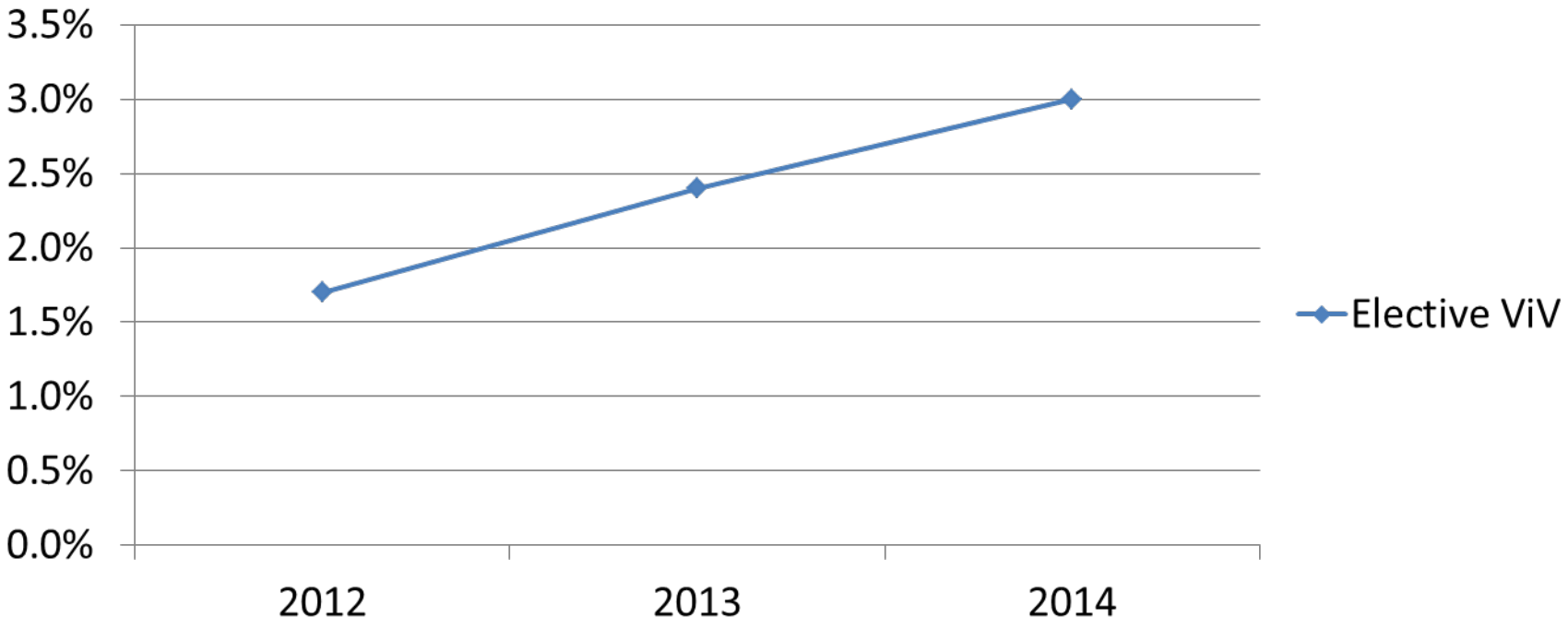
TAVR: Bleeding and Vascular Complications





A. *Is this related to lower risk patients being treated?*
B. *Is this related to improving site performance?*
C. *Is this related to next generation TAVR technology and the use of less alternative access?*
D. *All of the above.*
E. *None of the above.*

Elective Valve-in-Valve

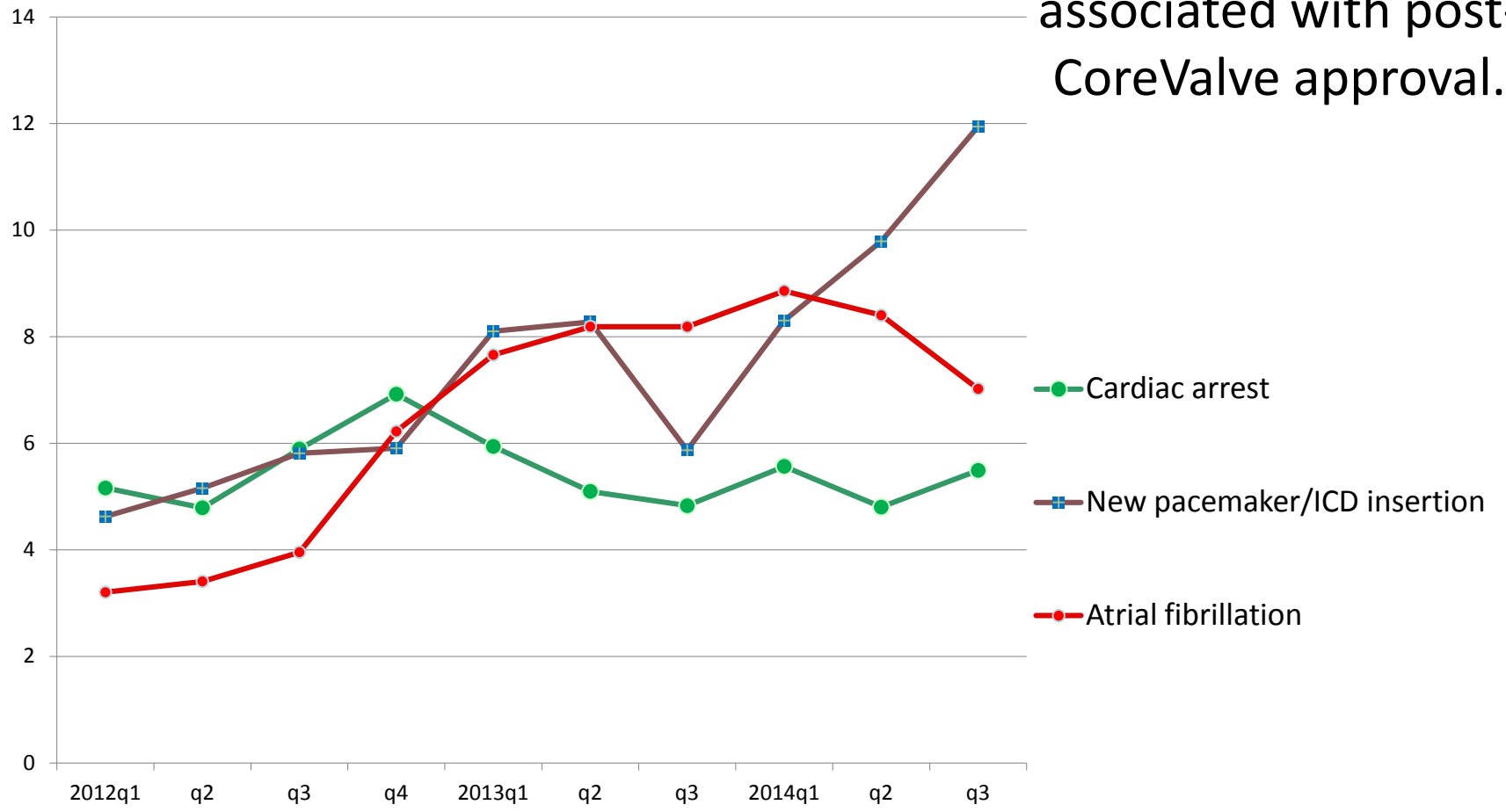


Source: STS/ACC TVT Registry Database
23,557 records from 2012q1-2014q3 as of 2-13-15

Cardiac Outcomes After TAVR

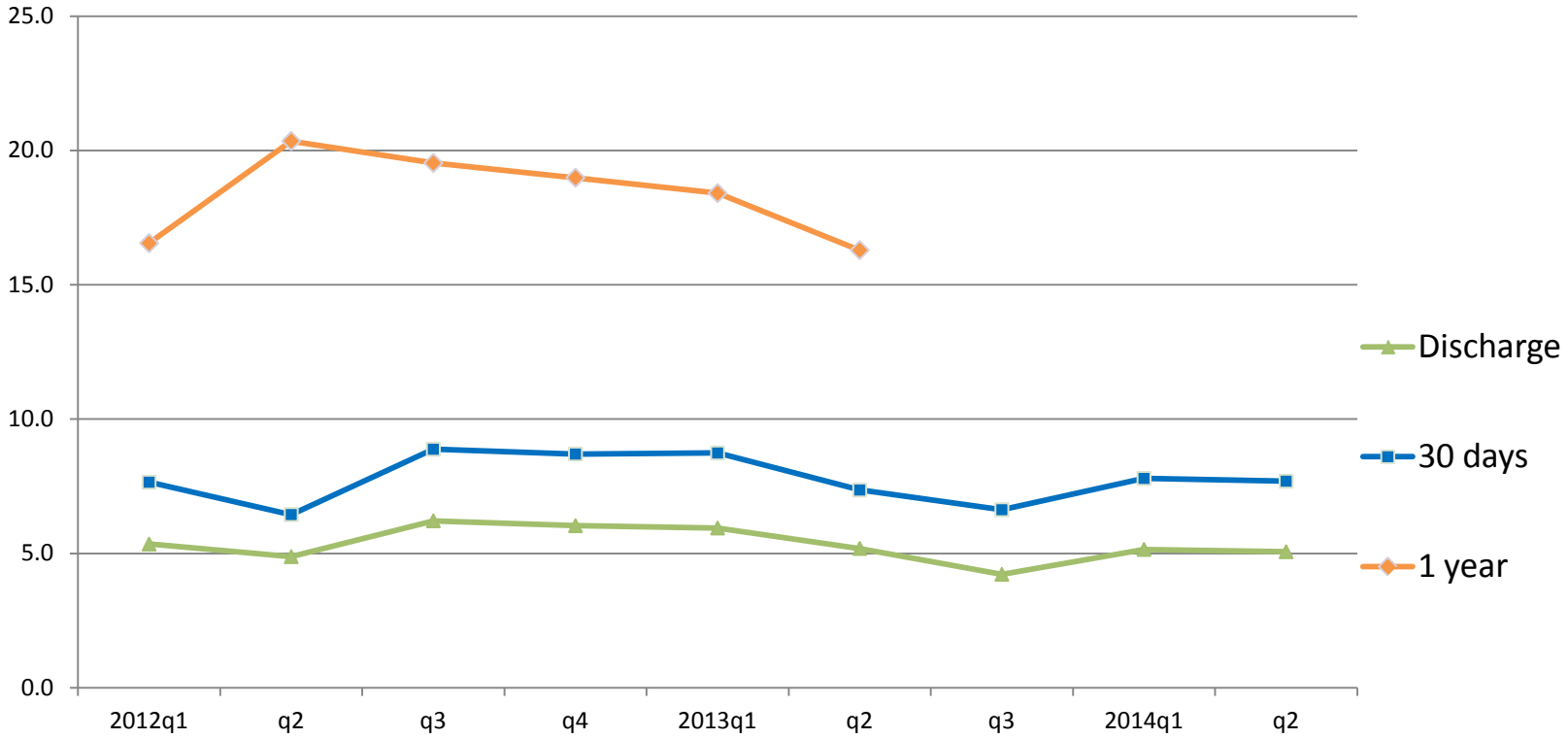
(in-hospital)

Pacemaker increase associated with post-CoreValve approval.



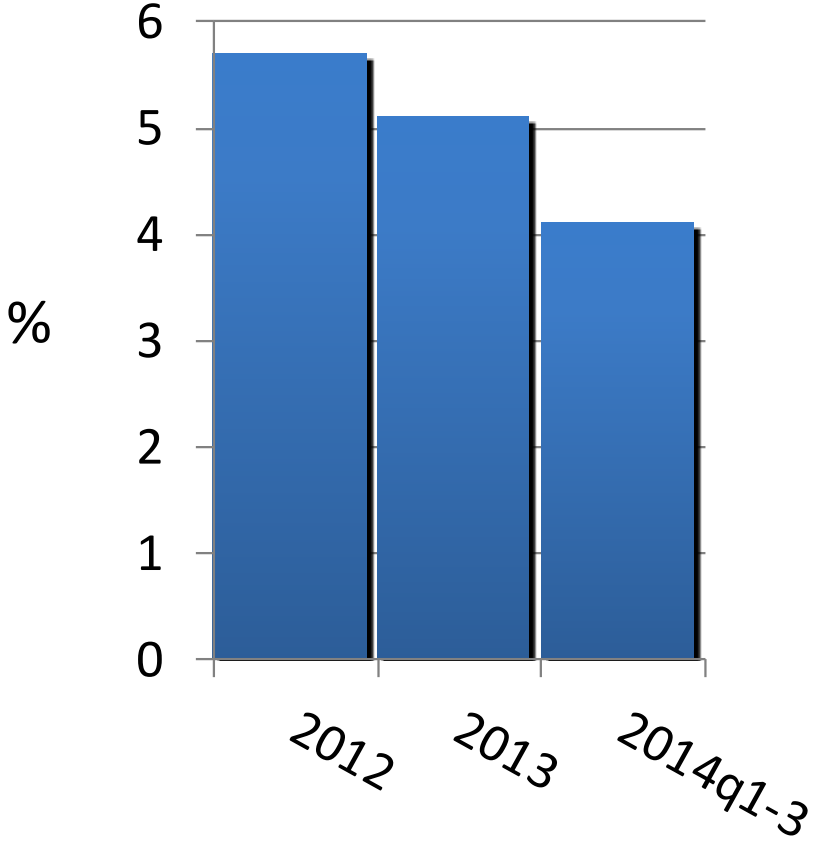
Source: STS/ACC TVT Registry Database
23,557 records from 2012q1-2014q3 as of 2-13-15

TAVR Mortality
all cause, site reported



Source: 19,063 records in the STS/ACC TVT Registry Database
Note: follow-up reported on 70% (30 day) and 60% (1 year) of records as of 2-13-15

TAVR: In-Hospital Mortality Decreasing

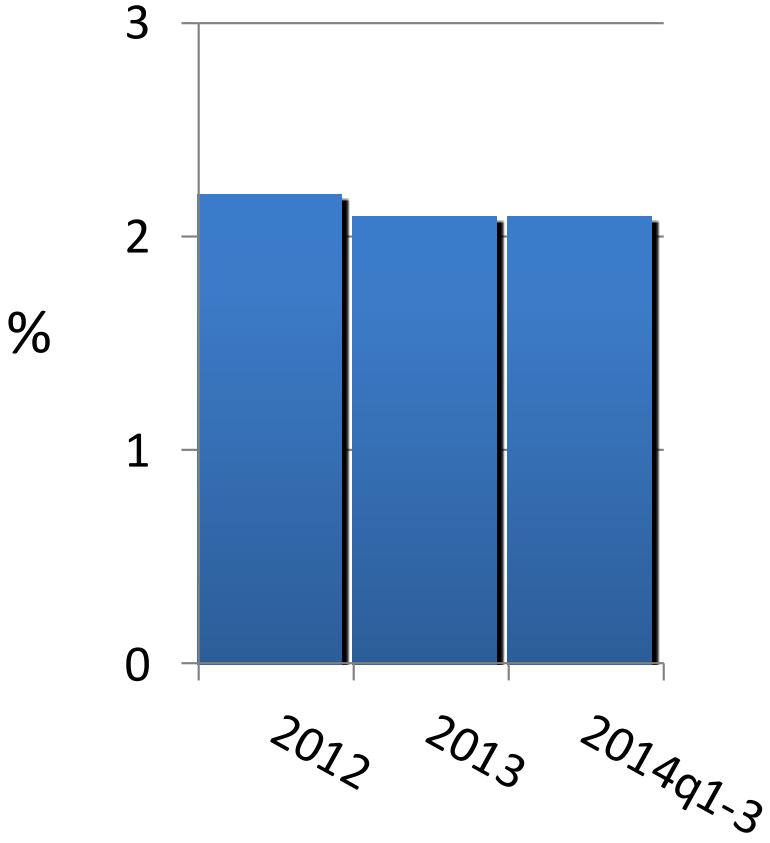


Explanation?

A. Related to treating lower risk patients.
B. Related to improved site performance.
C. Related to next generation TAVR technology.
D. None of the above.
E. All of the above.

Source: STS/ACC TVT Registry Database
23,557 records from 2012q1-2014q3 as of 2-13-15

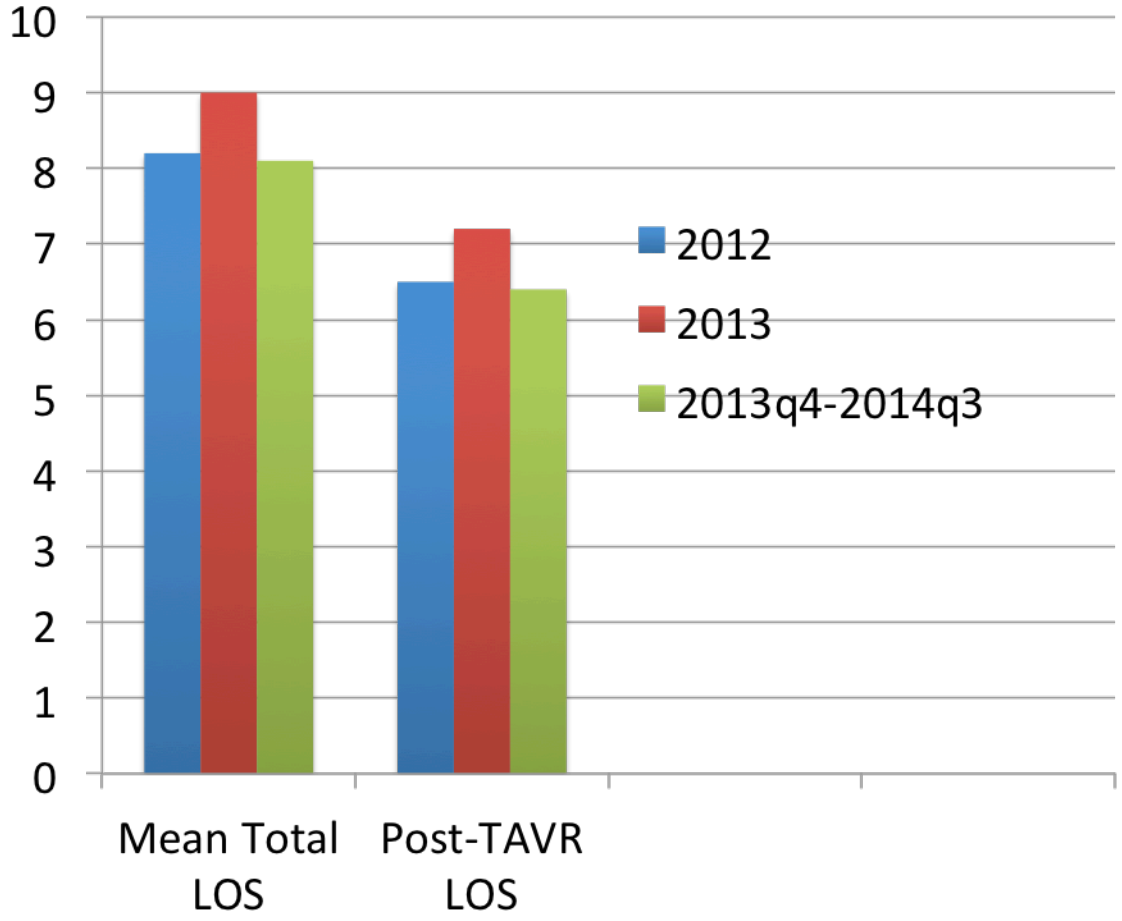
TAVR: Any Stroke During TAVR Hospitalization



- Is this meaningful ?
- How under-reported are strokes in the TVT Registry?
- Or is this a true reflection of the frequency of clinically apparent-important strokes?

Source: STS/ACC TVT Registry Database
23,557 records from 2012q1-2014q3 as of 2-13-15

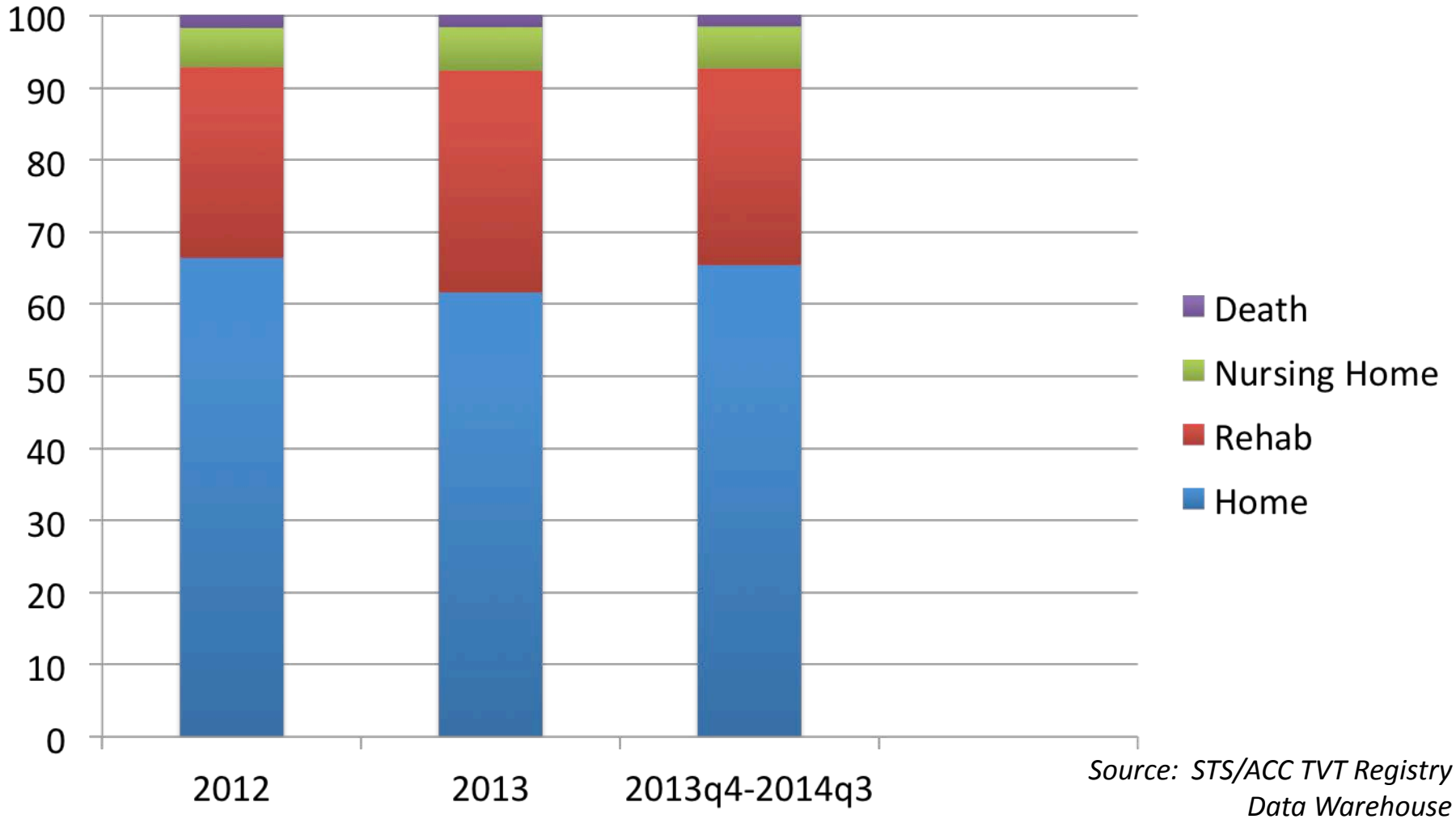
TAVR: Hospital Stay



- Surprisingly not much change over time despite more experience.
- Appears to parallel changes in access site with an ongoing elderly population of patients.

Source: STS/ACC TVT Registry Data Warehouse as of Nov-Dec 2014

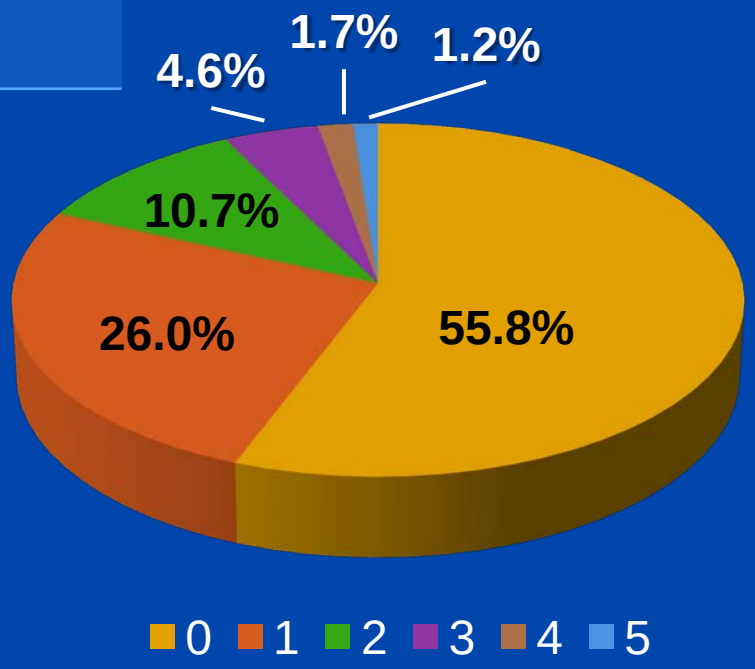
After TAVR – The "Disposition"



Source: STS/ACC TVT Registry Data Warehouse as of Nov-Dec 2014

TVT Registry
One Year Outcome

Mortality	**26.2% (24.7, 27.8%)**
Stroke	**3.6% (3.1%, 4.2%)**
Death or stroke	**28.4% (need info)**
Rehospitalization within 6 months	

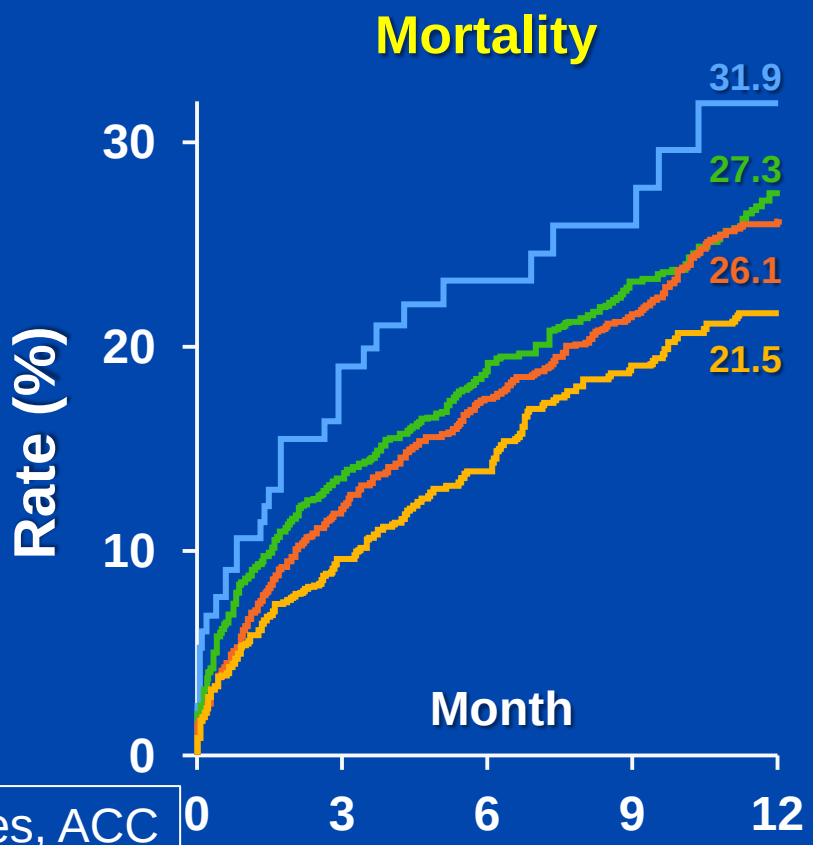


Holmes, ACC 2014
JAMA, In Press

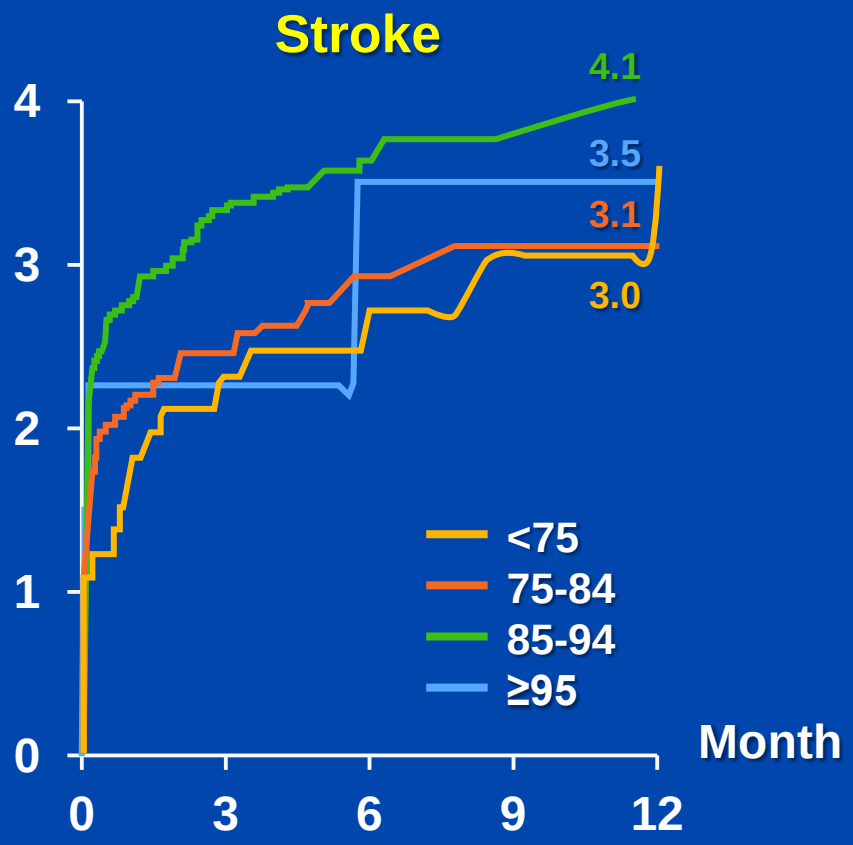
MAYO CLINIC

Cumulative Incidence of Death and Stroke

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



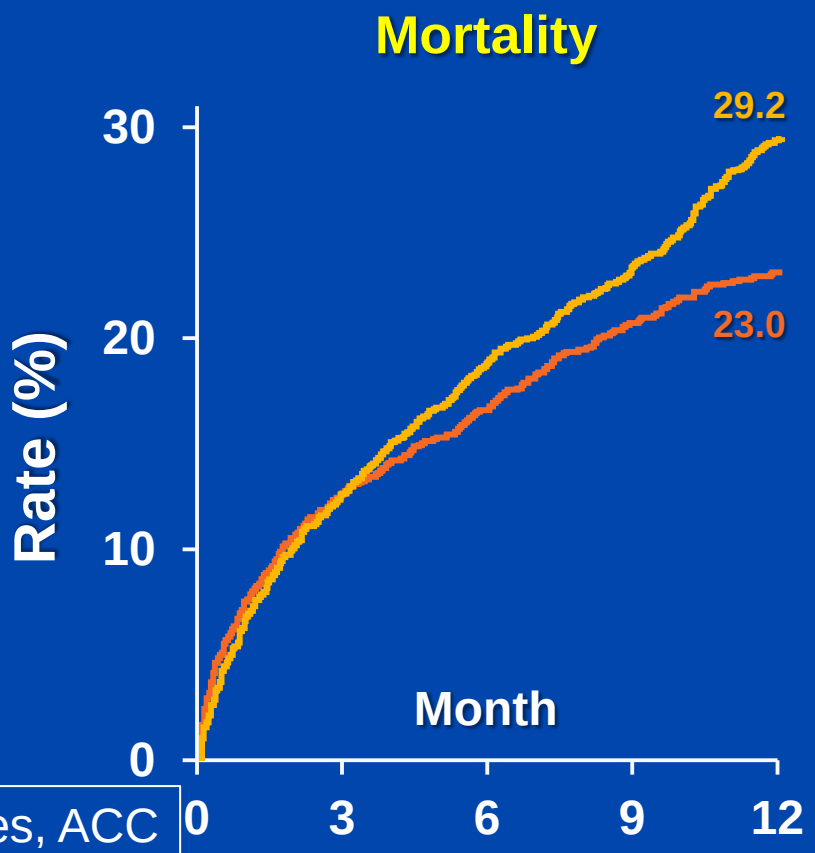
	HR	P
75-84 vs <75	0.999	0.998
85-94 vs <75	1.160	0.613
95+ vs <75	0.289	0.247

Holmes, ACC 2014
JAMA, In Press

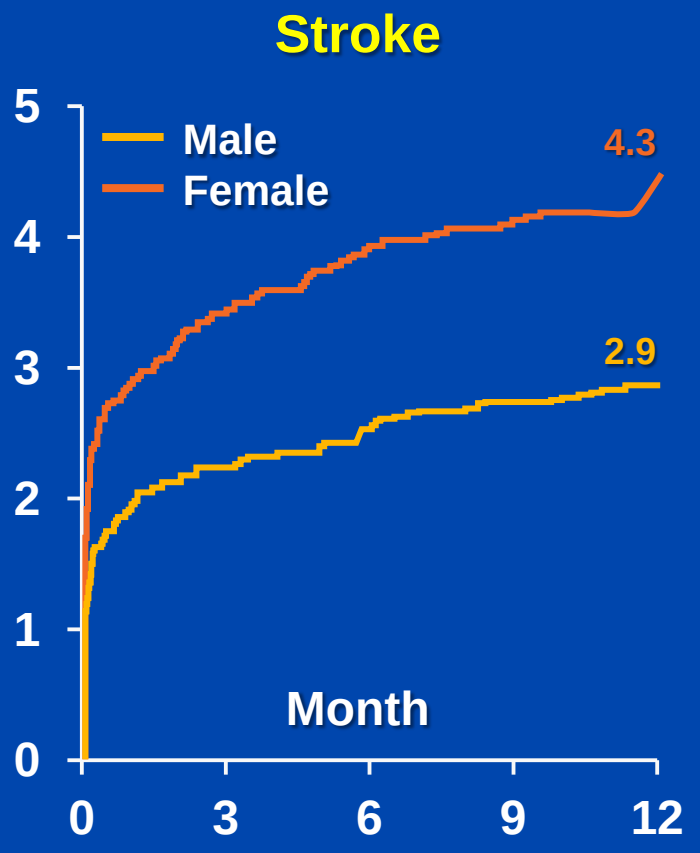
MAYO CLINIC

Cumulative Incidence of Death and Stroke

Sex



	HR	P
Male vs Female	1.189	0.007



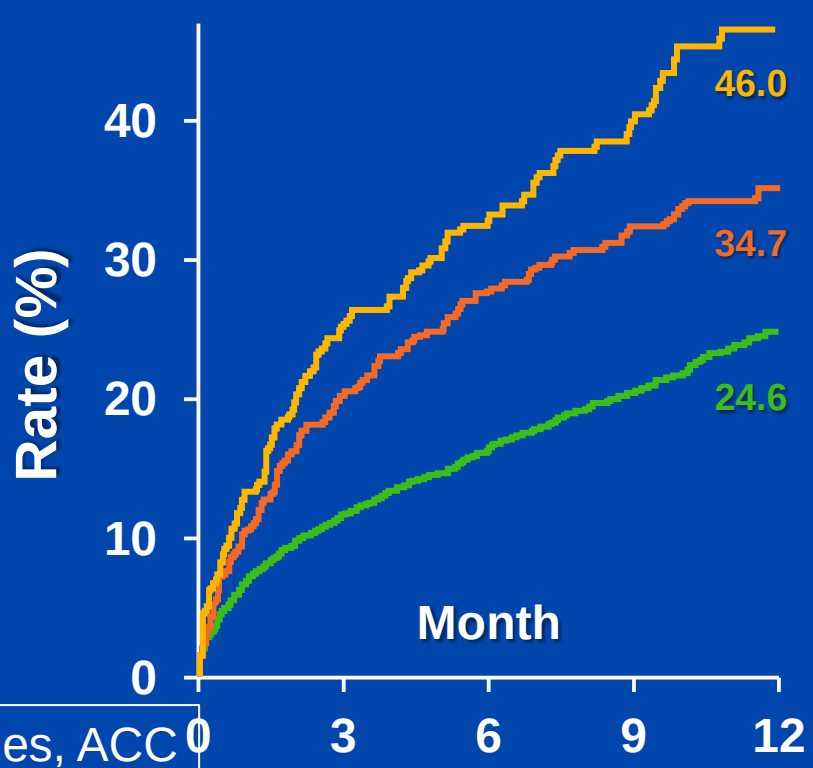
	HR	P
Male vs Female	0.655	0.012

Holmes, ACC 2014
JAMA, In Press

MAYO CLINIC

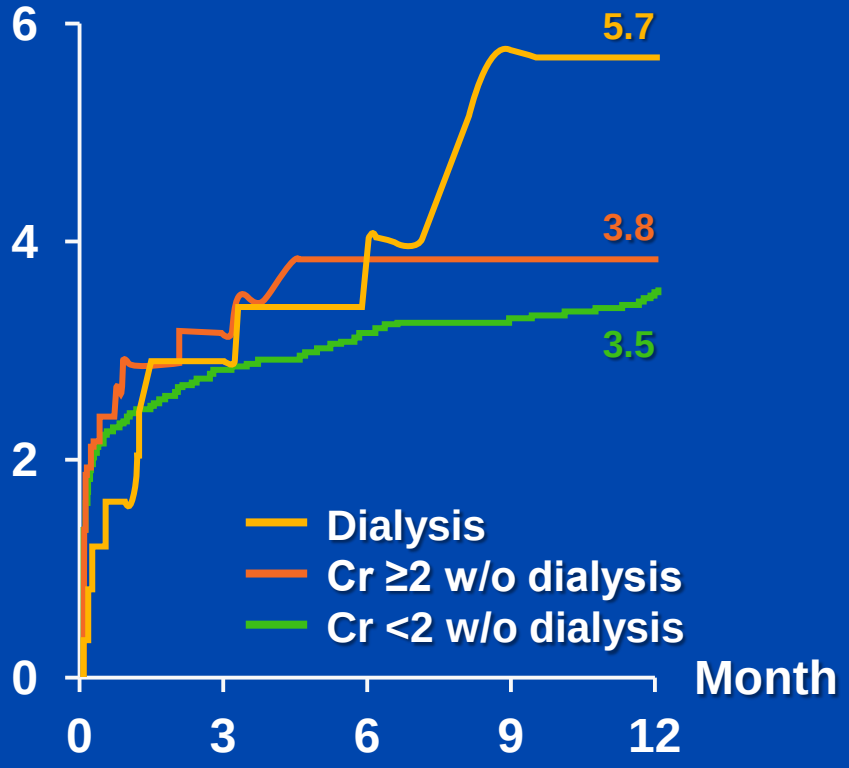
Cumulative Incidence of Death and Stroke
Renal Function

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

Holmes, ACC 2014
JAMA, In Press

MAYO CLINIC

How is TAVR Implemented in the U.S; Lessons from TVT Registry

- "Rational Dispersion" has largely occurred
- ~ 350 centers perform TAVR
- >30,000 patients have received TAVR in U.S. since approval
- In hospital mortality ~5%
- 30 day mortality ~ 7%
- One year mortality~ 25%
- Significant factors predictive of one year mortality have been identified
- One year stroke rate- 3.6% but likely under-reported