TAVR in Females

Susheel Kodali, MD

Director, Heart Valve Center

Director, Interventional Cardiology Fellowship Program

Columbia University Medical Center

Disclosure Statement of Financial Interest

Susheel Kodali, MD

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

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Edwards Lifesciences
• Steering Committee	• Edwards Lifesciences, Claret Medical, Meril
• SAB (Equity)	• Thubrikar Aortic Valve, Inc

Introduction

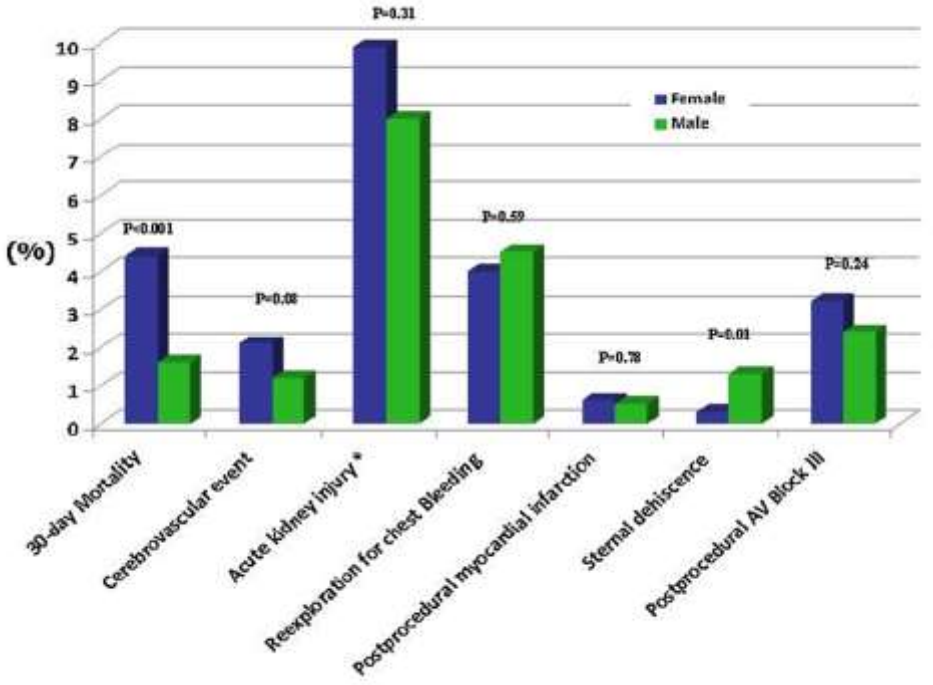
- Transcatheter aortic valve replacement (TAVR) has become an established treatment for high-risk patients with severe aortic stenosis.
- Female sex is associated with worse outcomes after PCI, SAVR and CABG
- TAVI is performed with equal frequency in men and women

Are the outcomes the same?

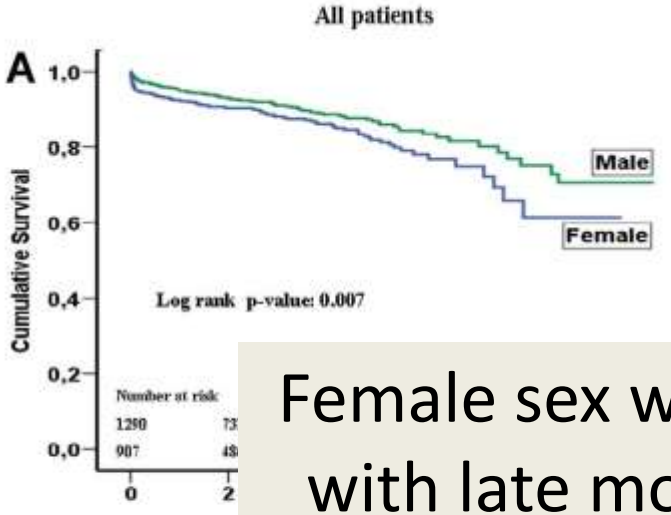
Sex-Related Differences in 2197 Patients Undergoing Isolated Surgical Aortic Valve Replacement

Yacine Elhmidi, M.D.,* Nicolo Piazza, M.D., Ph.D.,* Domenico Mazzitelli, M.D.,* Michael Wottke, M.D.,* Rüdiger Lange, M.D., Ph.D.,† and Sabine Bleiziffer, M.D.*

- Female patients comprised 41.3% of patients
- Female gender a predictor of 30 day mortality on univariate [HR – 2.8 (1.6-4.9)] and multivariate analysis [HR – 2.2 (0.98 – 5.2)]



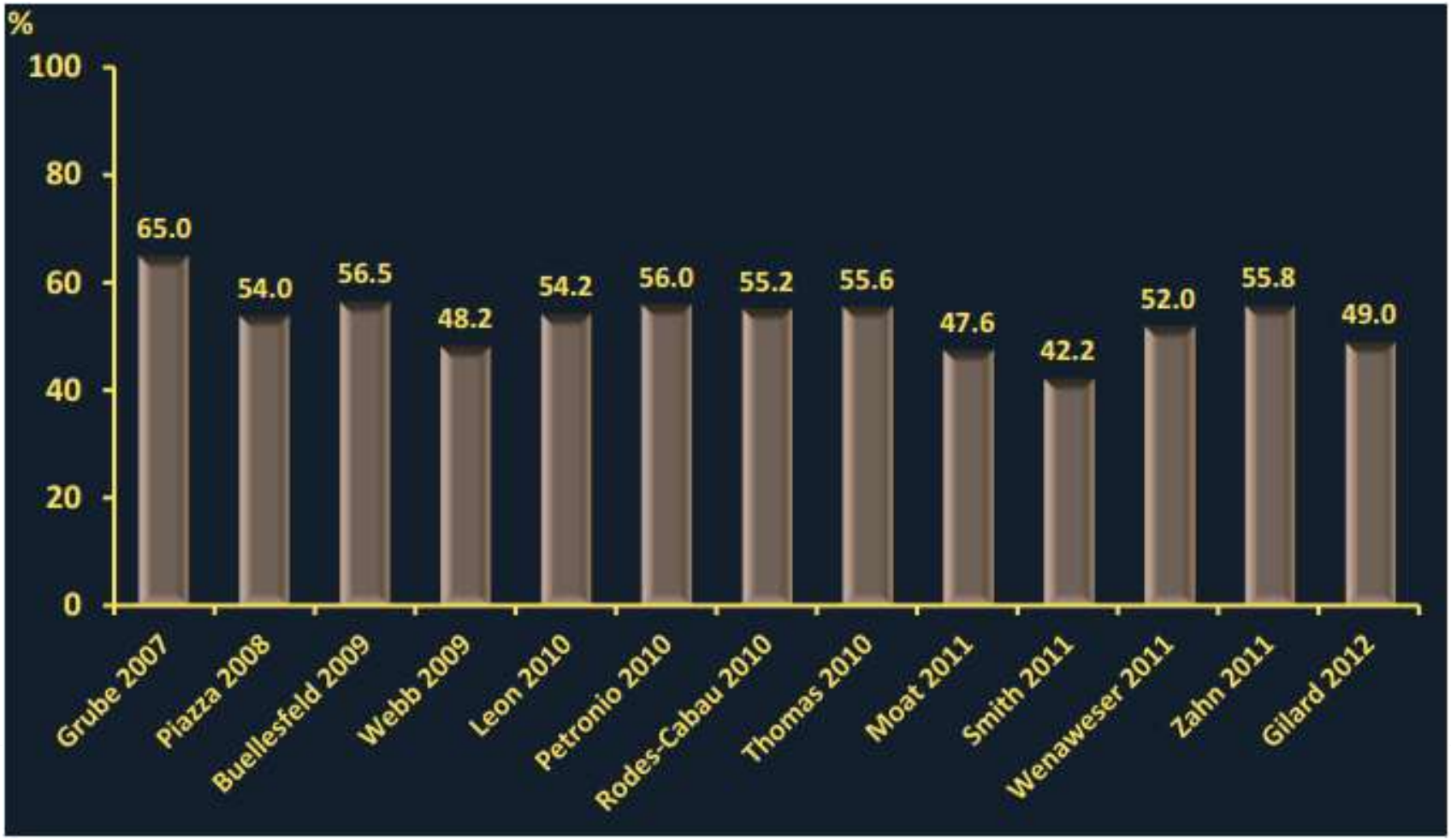
Impact of Female Sex on Late Outcomes after SAVR



Female sex was *weakly* associated with late mortality on univariate analysis [HR – 1.3 (1.03 – 1.7)] but not on multivariate analysis

Elhmidi et al, 2014

Frequency of female sex across TAVR studies



Circulation
Cardiovascular Interventions

American Heart Association®

Sex-Related Differences in Outcomes After Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-analysis

Zhen-Gang Zhao, Yan-Biao Liao, Yong Peng, Hua Chai, Wei Liu, Qiao Li, Xin Ren, Xue-Qin Wang, Xiao-Lin Luo, Chen Zhang, Li-Hui Lu, Qing-Tao Meng, Chi Chen, Mao Chen, Yuan Feng and De-Jia Huang

- 27 articles
- 9118 patients
  - 4176 Men
  - 4942 Women

Pooled Characteristics of Men and Women

Baseline Characteristics	Men	Women	*P* Value
Age	80.6±1.6 (n=933)	82.1±1.2 (n=1032)	<0.001
BMI	26±0.4 (n=333)	26.1±0.5 (n=335)	0.78
Hypertension, n/total (%)	564/774 (72.9)	711/886 (80.2)	0.31
Diabetes mellitus, n/total (%)	292/933 (31.3)	274/1032 (26.6)	0.03
COPD, n/total (%)	306/933 (38.6)	250/1032 (24.2)	0.006
NYHA class III or IV, n/total (%)	671/891 (75.3)	778/974 (79.9)	0.01
CAD, n/total (%)	588/774 (76.0)	459/886 (51.8)	<0.001
Previous MI, n/total (%)	320/933 (34.3)	201/1032 (19.5)	<0.001
Previous PCI, n/total (%)	411/933 (44.1)	282/1032 (27.3)	<0.001
PVD, n/total (%)	257/774 (33.2)	189/886 (21.3)	0.02
Previous stroke, n/total (%)	140/933 (15.0)	120/1032 (11.6)	0.06
Atrial fibrillation, n/total (%)	172/645 (26.7)	183/755 (24.2)	0.50
Logistic EuroSCORE	24.0±1.3 (n=621)	22.7±1.4 (n=703)	0.06

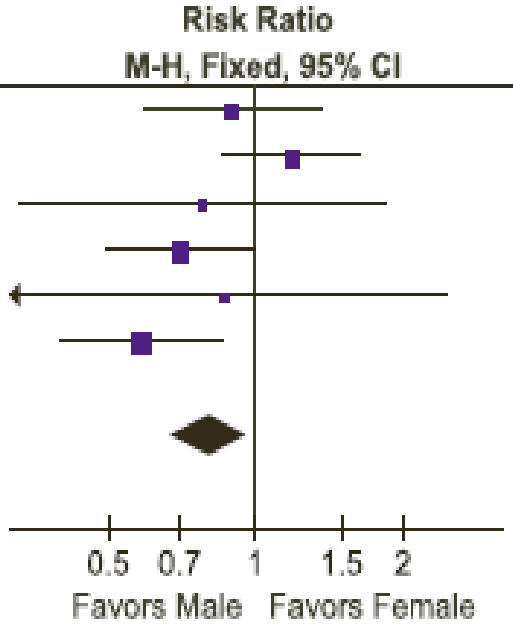
Zhen-Gang Zhao et al, Circ. Car Int - 2013

BLEEDING COMPLICATIONS

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Amabile 2012	26	80	33	91	13.9%	0.90 [0.59, 1.36]
Buchanan 2011	57	159	44	146	20.6%	1.19 [0.86, 1.64]
Buja 2013	8	291	13	368	5.2%	0.78 [0.33, 1.85]
Humphries 2012	44	312	66	329	28.9%	0.70 [0.50, 1.00]
Stangl 2012	5	42	8	58	3.0%	0.86 [0.30, 2.45]
Van Mieghem 2012	39	519	60	467	28.4%	0.58 [0.40, 0.86]
Total (95% CI)		**1403**		**1459**	**100.0%**	**0.81 [0.68, 0.96]**
Total events	179		224			

Heterogeneity: $Chi^2 = 9.14$, $df = 5$ ($P = 0.10$); $I^2 = 45\%$

Test for overall effect: $Z = 2.42$ ($P = 0.02$)



Men had a significantly lower risk for major/life-threatening bleeding (pooled RR, 0.81; 95% confidence interval [CI], 0.68–0.96)

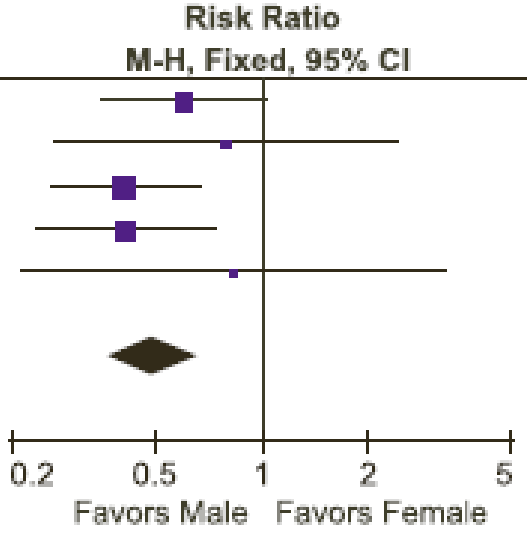
Zhen-Gang Zhao et al, Circ. Car Int - 2013

VASCULAR COMPLICATIONS

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buchanan 2011	19	159	29	146	24.2%	0.60 [0.35, 1.03]
Buja 2013	5	291	8	368	5.6%	0.79 [0.26, 2.39]
Genereux 2012	21	227	43	192	37.2%	0.41 [0.25, 0.67]
Humphries 2012	15	312	38	329	29.6%	0.42 [0.23, 0.74]
Stangl 2012	3	42	5	58	3.4%	0.83 [0.21, 3.28]
Total (95% CI)		**1031**		**1093**	**100.0%**	**0.49 [0.37, 0.66]**
Total events	63		123			

Heterogeneity: Chi² = 2.62, df = 4 (P = 0.62); I² = 0%

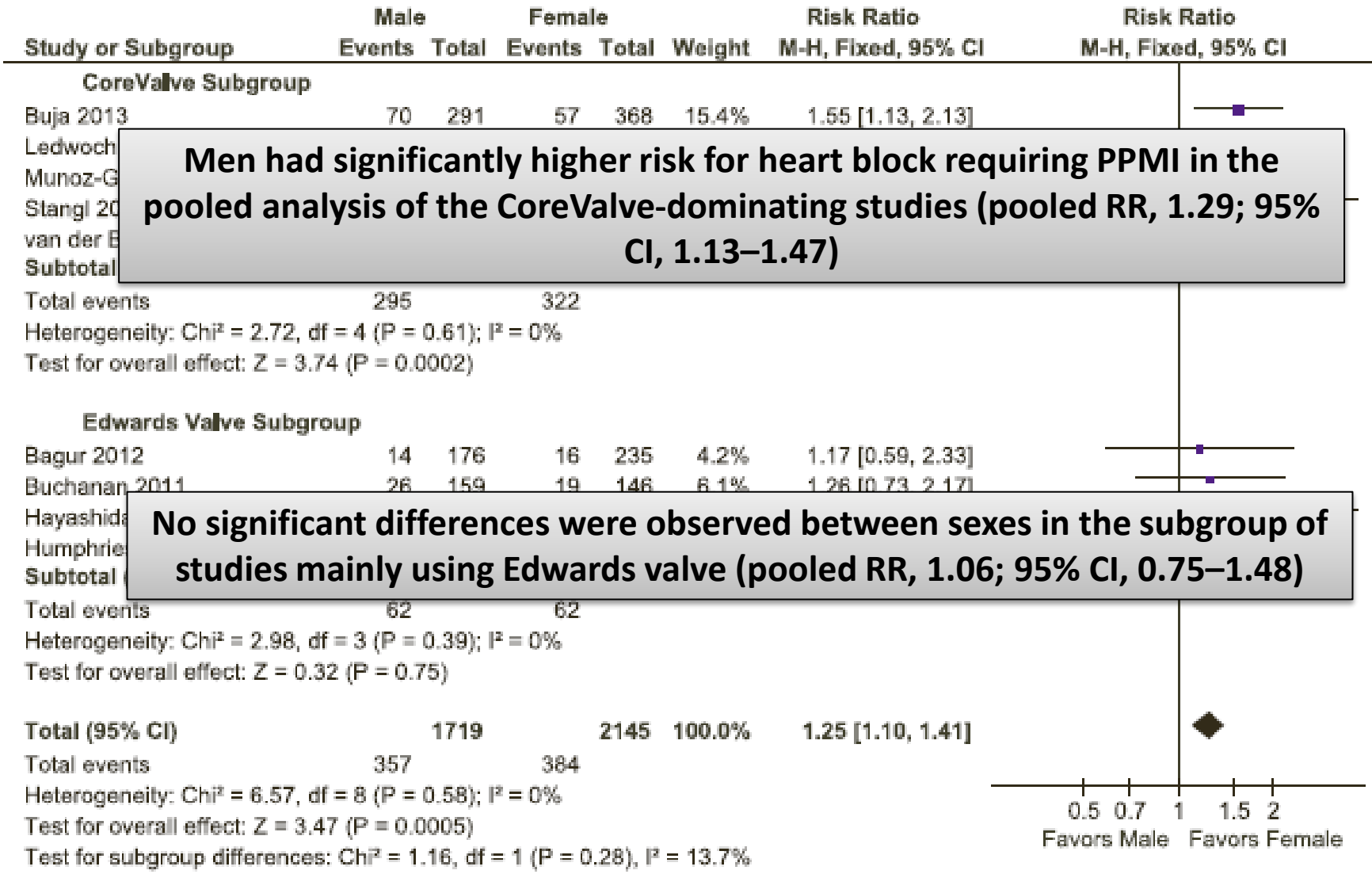
Test for overall effect: Z = 4.82 (P < 0.00001)



Pooled results suggested a significantly lower risk of major vascular complication in men (pooled RR, 0.49; 95% CI, 0.37–0.66)

Zhen-Gang Zhao et al, Circ. Car Int - 2013

PACEMAKER IMPLANTATION



Men had significantly higher risk for heart block requiring PPMI in the pooled analysis of the CoreValve-dominating studies (pooled RR, 1.29; 95% CI, 1.13–1.47)

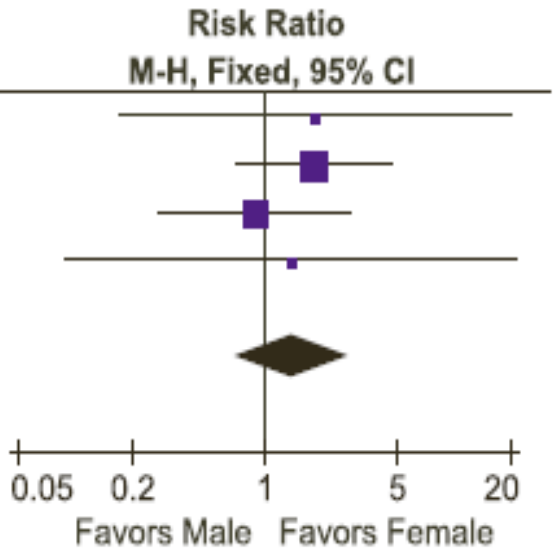
No significant differences were observed between sexes in the subgroup of studies mainly using Edwards valve (pooled RR, 1.06; 95% CI, 0.75–1.48)

STROKE

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buchanan 2011	2	159	1	146	7.5%	1.84 [0.17, 20.04]
Buja 2013	10	291	7	368	44.5%	1.81 [0.70, 4.69]
Humphries 2012	5	312	6	329	42.0%	0.88 [0.27, 2.85]
Stangl 2012	1	42	1	58	6.0%	1.38 [0.09, 21.46]
Total (95% CI)		**804**		**901**	**100.0%**	**1.39 [0.71, 2.74]**
Total events	18		15			

Heterogeneity: Chi² = 0.93, df = 3 (P = 0.82); I² = 0%

Test for overall effect: Z = 0.96 (P = 0.34)



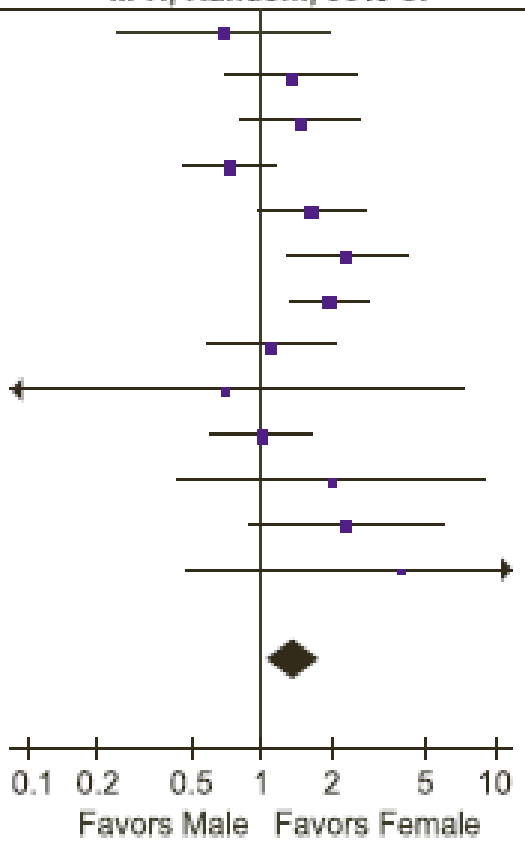
No significant sex differences with regard to the risk of stroke after TAVI (pooled RR, 1.39; 95% CI, 0.71–2.74)

30-DAY MORTALITY

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Risk Ratio M-H, Random, 95% CI
Buchanan 2011	6	159	8	146	4.6%	0.69 [0.24, 1.94]
Buja 2013	18	291	17	368	8.7%	1.34 [0.70, 2.55]
Hayashida 2012	23	129	16	131	9.7%	1.46 [0.81, 2.63]
Houthuizen 2012	27	319	42	360	12.3%	0.73 [0.46, 1.15]
Humphries 2012	31	312	20	329	10.6%	1.63 [0.95, 2.81]
Lange 2012	23	155	17	265	9.6%	2.31 [1.28, 4.19]
Lauten 2012	60	544	43	758	14.3%	1.94 [1.34, 2.83]
Rodes-Cabau 2010	17	152	19	187	9.2%	1.10 [0.59, 2.04]
Stangl 2012	1	42	2	58	1.1%	0.69 [0.06, 7.37]
Van Mieghem 2012	30	519	27	467	11.3%	1.00 [0.60, 1.66]
Ye 2009	4	13	2	13	2.4%	2.00 [0.44, 9.08]
Yong 2012	9	47	6	72	5.1%	2.30 [0.88, 6.03]
Zhao 2012	4	24	1	24	1.3%	4.00 [0.48, 33.22]
Total (95% CI)		**2706**		**3178**	**100.0%**	**1.37 [1.07, 1.76]**
Total events	253		220			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 20.45$, df = 12 (P = 0.06); $I^2 = 41\%$

Test for overall effect: Z = 2.47 (P = 0.01)



Male sex was associated with a significantly higher risk for death at 30 days after TAVI as shown by the pooled results using a random-effects model (pooled RR, 1.37; 95% CI, 1.07–1.76)

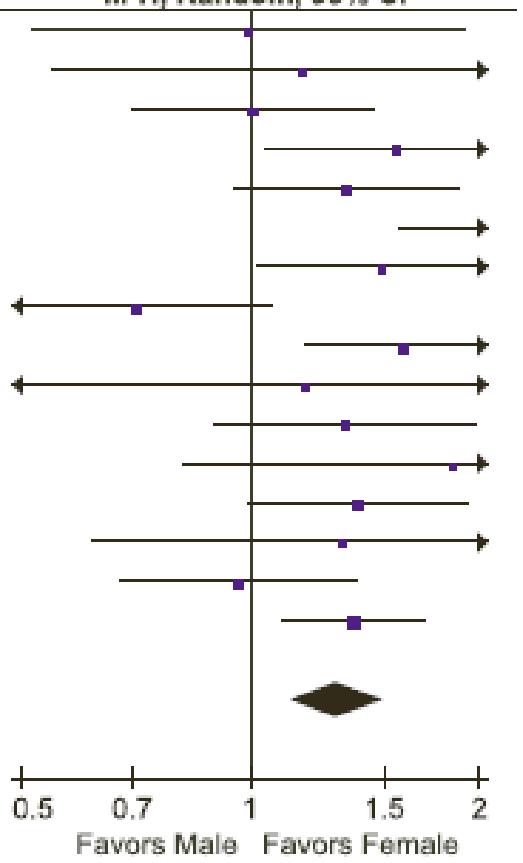
Zhen-Gang Zhao et al, Circ. Car Int - 2013

1-YEAR MORTALITY

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Risk Ratio M-H, Random, 95% CI
Amabile 2012	14	80	16	91	3.5%	1.00 [0.52, 1.91]
Buchanan 2011	14	159	11	146	2.7%	1.17 [0.55, 2.49]
Buja 2013	44	291	55	368	7.8%	1.01 [0.70, 1.46]
Elhmidi 2011	37	139	40	234	7.1%	1.56 [1.05, 2.31]
Genereux 2012	65	227	41	192	8.4%	1.34 [0.95, 1.88]
Gotzmann 2012	31	91	13	107	4.2%	2.80 [1.56, 5.03]
Hayashida 2012	47	129	32	131	7.5%	1.49 [1.02, 2.18]
Houthuizen 2012	34	319	54	360	7.0%	0.71 [0.48, 1.06]
Humphries 2012	86	312	57	329	9.6%	1.59 [1.18, 2.14]
Munoz-Garcia 2012	5	50	7	83	1.4%	1.19 [0.40, 3.54]
Rodes-Cabau 2010	39	152	36	187	7.0%	1.33 [0.89, 1.99]
Rodes-Cabau 2011	11	43	8	58	2.4%	1.85 [0.82, 4.21]
Seiffert 2012	51	145	46	181	8.6%	1.38 [0.99, 1.93]
Sinning 2010	11	37	9	40	2.7%	1.32 [0.62, 2.82]
Tamburino 2011	45	292	59	371	8.0%	0.97 [0.68, 1.38]
Zahn 2013	129	547	133	771	12.2%	1.37 [1.10, 1.70]
Total (95% CI)		**3013**		**3649**	**100.0%**	**1.30 [1.14, 1.49]**
Total events	663		617			

Heterogeneity: Tau² = 0.03; Chi² = 24.72, df = 15 (P = 0.05); I² = 39%

Test for overall effect: Z = 3.79 (P = 0.0002)



One-year mortality of men and women was 22.0% and 16.9%, respectively.

Pooled analysis using a random-effects model showed that men had significantly higher 1-year mortality (pooled RR, 1.30; 95% CI, 1.14–1.49;

Zhen-Gang Zhao et al, Circ. Car Int - 2013

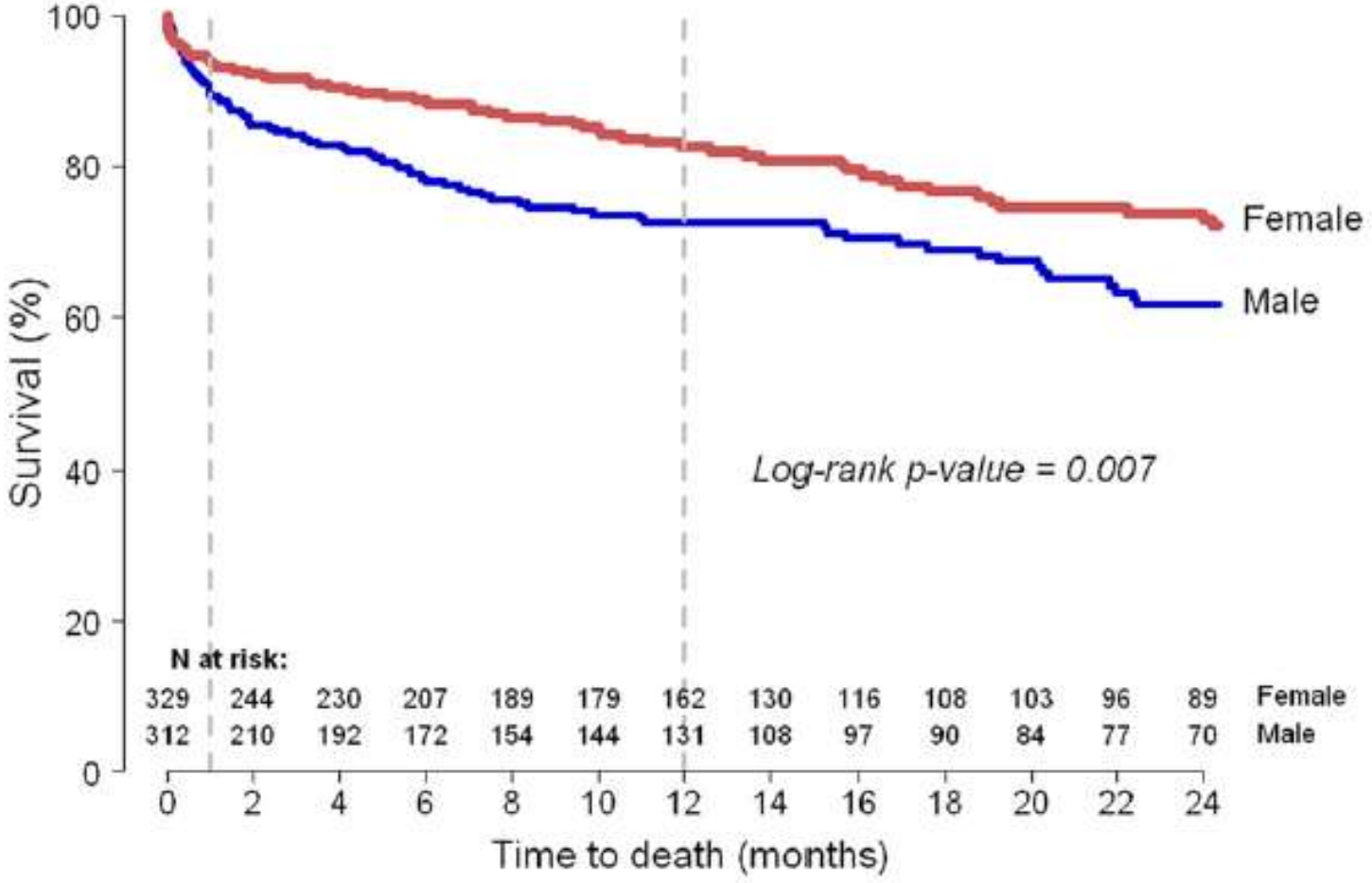
30-Day Post-Procedural Outcomes

Event	Total (n = 584)*	Female (n = 306)	Male (n = 278)	p Value
Major vascular complication	53 (8.6)	38 (12.4)	15 (5.4)	0.003
Major/life-threatening bleed	110 (17.3)	66 (21.6)	44 (15.8)	0.08
Blood transfusion	39 (6.7)	29 (9.5)	10 (3.6)	0.005
Major stroke	11 (1.9)	6 (2.0)	5 (1.8)	0.89
New pacemaker	32 (5.5)	20 (6.4)	12 (4.3)	0.24
30-day mortality	51 (8.7)	20 (6.5)	31 (11.2)	0.05

Values are n (%). *Excluded 57 cases without 30 days of follow-up.

- Higher vascular and bleeding complications in women
- Higher need for blood transfusions in women
- Higher 30-day mortality in males

2-Year Survival



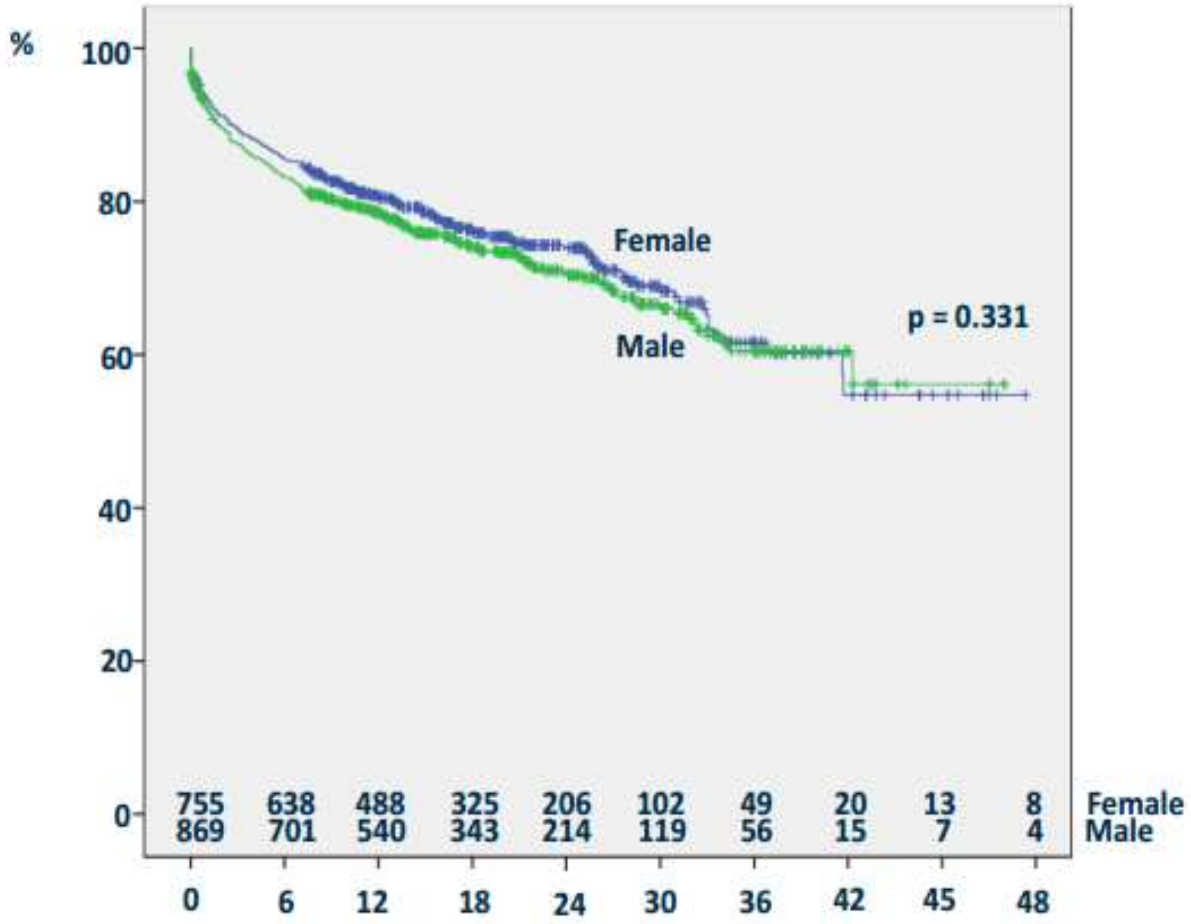
- **Better survival** in women (72.5% Vs. 61.7%; p = 0.007)
- After adjustment for age, site, and access route, the female HR was 0.58 (95% CI: 0.41 to 0.82; p = 0.002)

Influence of Gender on Clinical Outcomes Following Transcatheter Aortic Valve Implantation from the UK Transcatheter Aortic Valve Implantation Registry and the National Institute for Cardiovascular Outcomes Research

Rasha Al-Lamee, MA, MBBS, Christopher Broyd, BSc, MBBS, Jessica Parker, RGN, Justin E. Davies, MBBS, PhD, Jamil Mayet, MBChB, MD, Nilesh Sutaria, MBChB, MD, Ben Ariff, MBBS, PhD, Beth Unsworth, PhD, Jonathan Cousins, BSc, MBBS, Colin Bicknell, BSc, MBBS, Jonathan Anderson, MBChB, Iqbal S. Malik, MBBCh, PhD, Andrew Chukwuemeka, MBBS, MD, Daniel J. Blackman, MBChB, MD, Neil Moat, MBBS, Peter F. Ludman, MBBChir, MD, Darrel P. Francis, MBBChir, MD, Ghada W. Mikhail, MBBS, MD

- UK National Registry
- 756 women vs. 871 men
- ESV and MCV used
- All events were defined according to Valve Academic Research Consortium criteria.

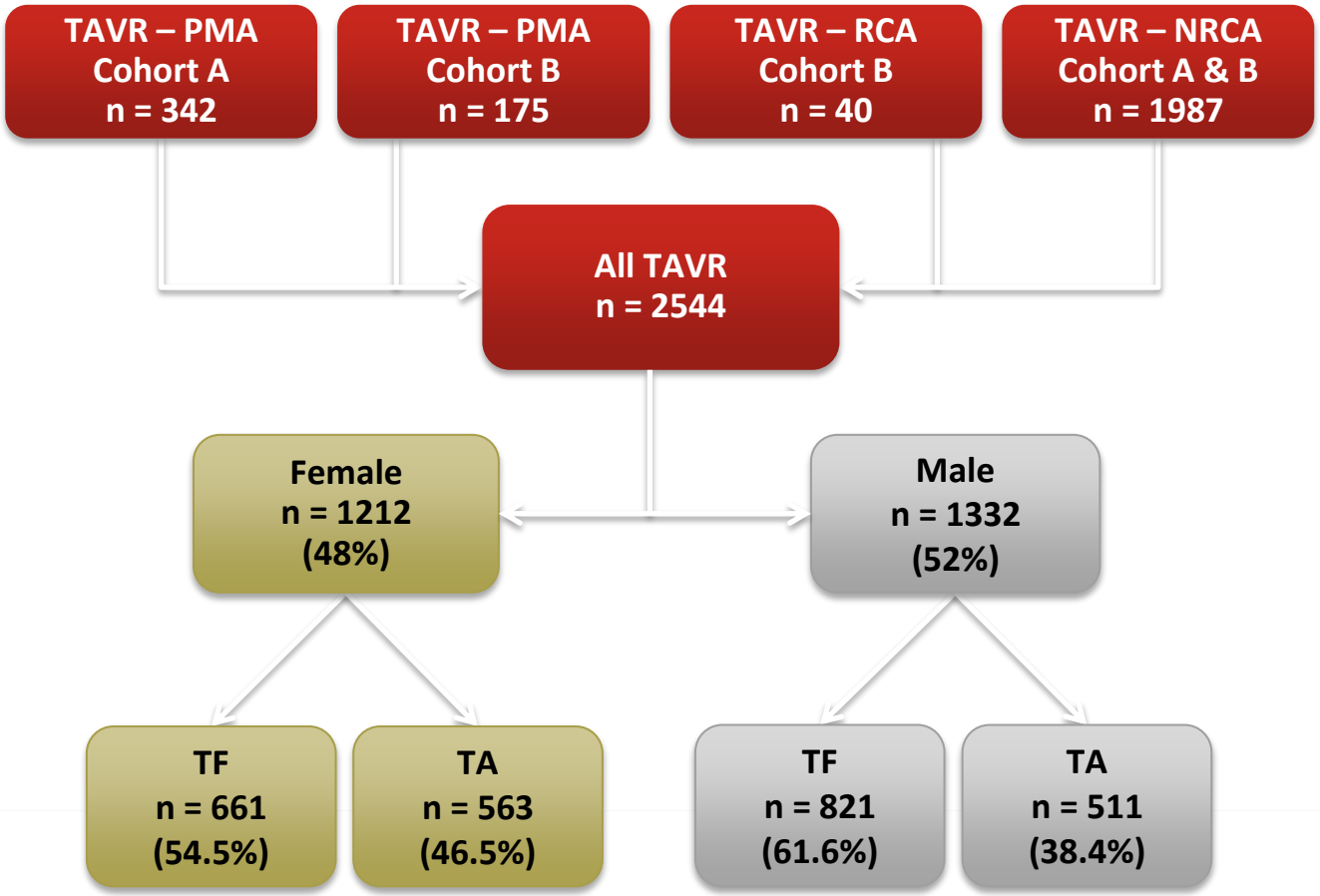
2-Year Survival



- **Higher rate** of vascular complications in Women
- **No differences** in 30-day and long-term survival between genders

Impact of Sex on Outcomes Following Transcatheter Aortic Valve Replacement in Patien with Severe Aortic Stenosis:

Insights From The PARTNER Experience



Patient Characteristics

Characteristic	Male (N = 1332)	Female (N = 1212)	p-value
Age (yr)	84.1 ± 7.3	84.9 ± 6.9	0.002
STS Score	11.2 ± 4.3	11.9 ± 4.2	<0.0001
Logistic EuroSCORE	27.8 ± 16.6	25.1 ± 15.7	<0.0001
Body Surface Area (BSA)	1.93 ± 0.21	1.66 ± 0.21	<0.0001
Diabetes - %	40.8	33.3	0.0001
Hyperlipidemia - %	87.0	80.1	<0.0001
Hypertension - %	90.5	93.2	0.02
Smoking - %	60.5	35.0	<0.0001
COPD - %	45.0	41.5	0.07
Pulmonary Hypertension - %	37.5	40.5	0.14
Renal Disease (CR > 2)	20.6	12.3	<0.0001

Patient Characteristics

Characteristic	Male (N = 1332)	Female (N = 1212)	p-value
CAD - %	87.5	67.1	<0.0001
Previous MI - %	33.4	17.9	<0.0001
Prior PCI - %	44.2	35.0	<0.0001
Prior CABG - %	59.3	24.2	<0.0001
Cerebrovascular Disease - %	27.8	24.7	0.08
Peripheral Vascular Disease - %	46.3	39.0	0.0002
Cardiomyopathy - %	20.3	10.7	<0.0001
Permanent Pacemaker - %	26.6	15.8	<0.0001

Baseline Echocardiography

Echo Findings	Male (n=1272)	Female (n=1162)	p-value
AVA - cm2	0.68 ± 0.19	0.61 ± 0.18	<0.0001
AVA Index	0.36 ± 0.10	0.37 ± 0.11	0.0002
AVG - mm Hg	42.0 ± 13.7	45.9 ± 14.7	<0.0001
Mean LVEF - %	49.8 ± 13.2	55.5 ± 11.9	<0.0001
Stroke Volume	71.8 ± 21.9	58.9 ± 17.2	<0.0001

30 Day Outcomes (1)

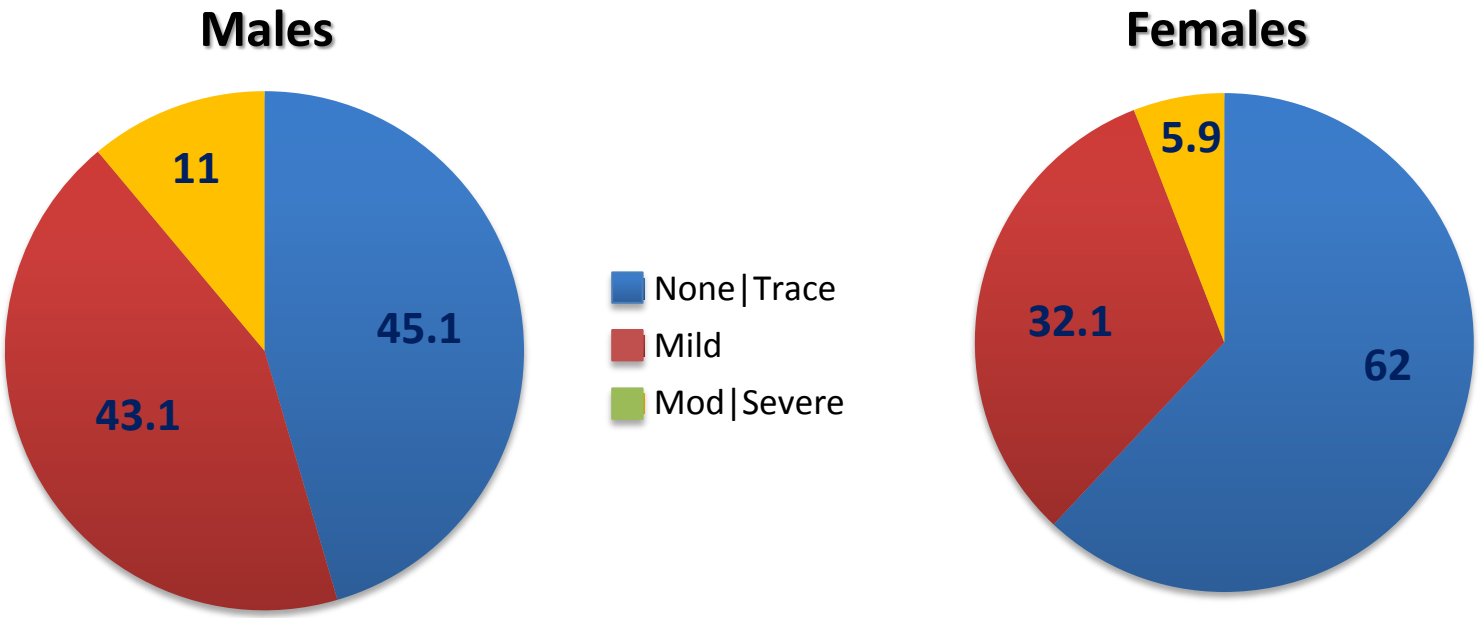
Outcome	Male	Female	p-value
All Cause Mortality – no. (%)	79 (5.9%)	79 (6.5%)	0.52
Cardiac mortality – no. (%)	52 (3.9%)	59 (4.9%)	0.23
Rehospitalization – no. (%)	87 (6.8%)	68 (5.9%)	0.37
Death or rehosp – no. (%)	165 (12.4%)	147 (12.1%)	0.90
Stroke	40 (3.0%)	46 (3.9%)	0.26
MI – no. (%)	12 (0.9%)	10 (0.8%)	0.85
Acute kidney inj* – no. (%)	49 (3.8%)	26 (2.2%)	0.03
Permanent Pacemaker – no (%)	67 (5.1%)	78 (6.6%)	0.11

* Renal replacement therapy

30 Day Outcomes (2)

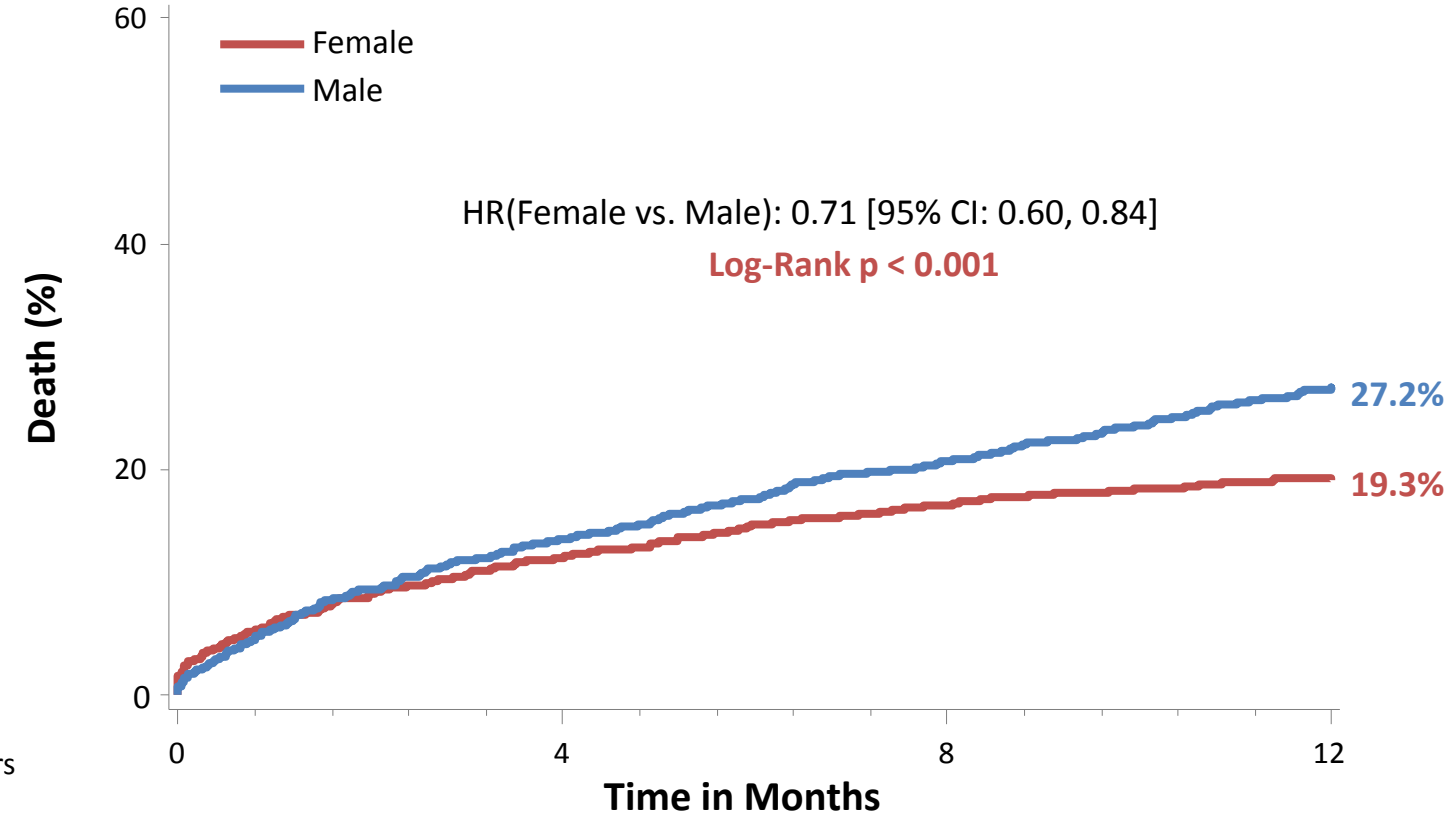
Outcome	Male	Female	p-value
Vascular complications			
All – no. (%)	133 (10.0%)	211 (17.5%)	<0.0001
Major – no. (%)	55 (4.1%)	103 (8.5%)	<0.0001
Major bleeding – no. (%)	103 (7.8%)	124 (10.3%)	0.03
Unplanned Arterial Procedure	97 (7.3%)	170 (14.0%)	<0.0001

Paravalvular Aortic Regurgitation



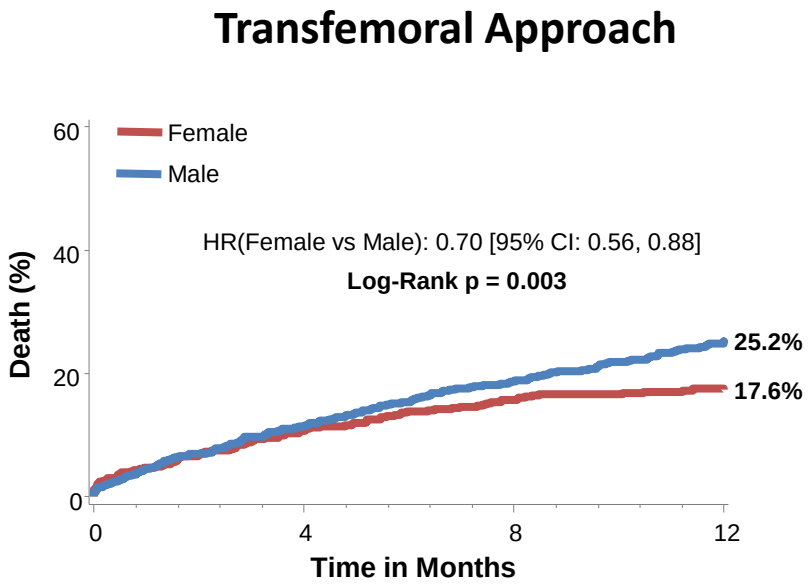
Males had significantly more paravalvular aortic regurgitation than Females ($p<0.01$ for all groups)

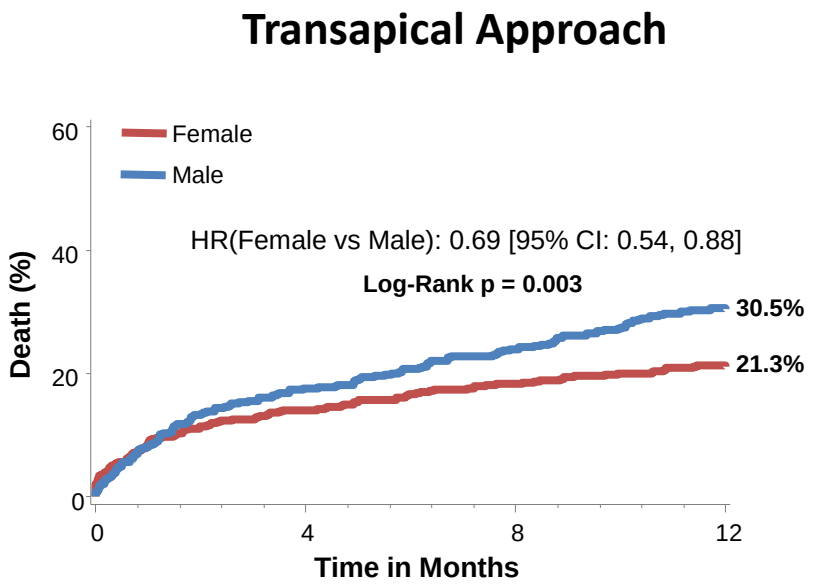
One Year Mortality Following TAVR



Numbers at Risk				
Female	1212	1045	878	669
Male	1332	1133	926	667

Impact of Treatment Approach on Mortality



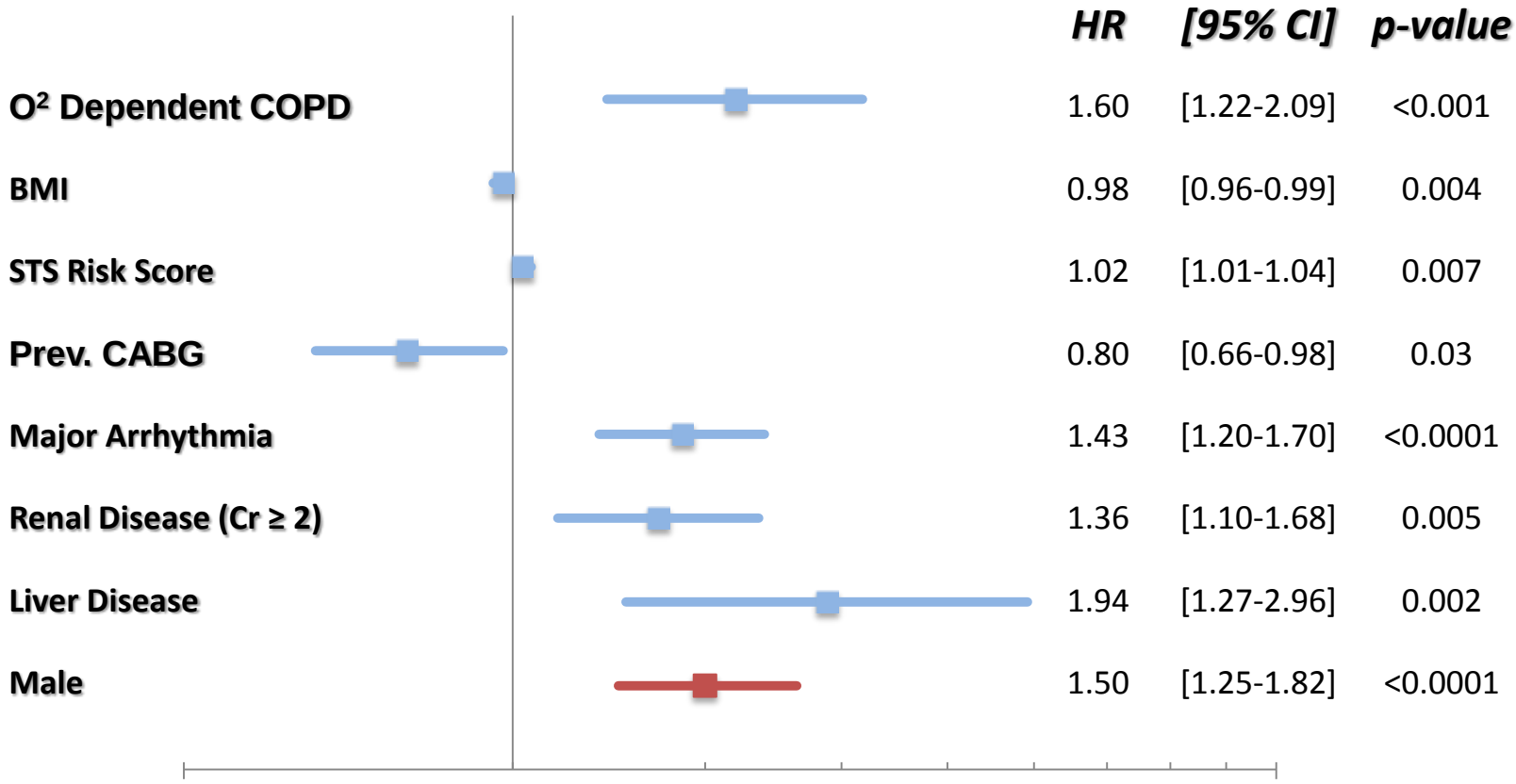


Number at risk

Female	649	575	491	399	563	470	387	270
Male	821	721	603	456	511	412	323	211

There was no interaction between treatment approach and sex (p_{INT} = 0.90)

Baseline Predictors of One Year Mortality



Potential Covariates: Male, Age, BMI, STS Risk Score, Diabetes, Smoker, Prior CABG, Prior BAV, Cardiomyopathy, Frailty, Major Arrhythmia, Permanent Pacemaker, Renal Disease, Liver Disease, COPD

What have we learned?

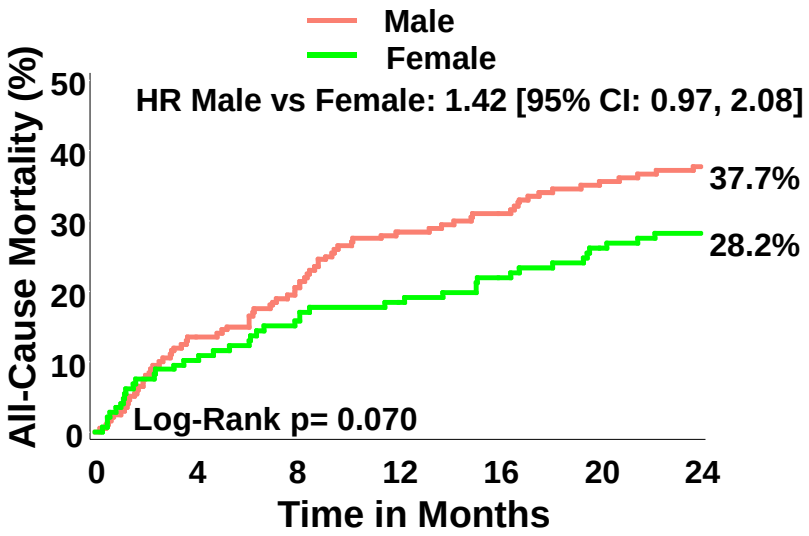
- Risk profiles of females and males undergoing TAVR are different
- Females have more vascular and bleeding complications but 30 day mortality is similar
- Although conflicting data does exist (UK registry), most studies demonstrate lower one year mortality following TAVR in females

How does TAVR compare to surgery among females and males?

2 year All-Cause Mortality (Cohort A)

THE PARTNER TRIAL

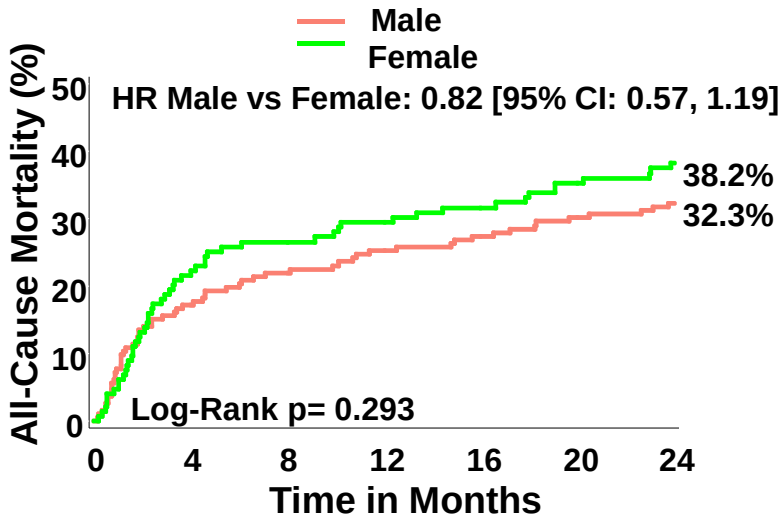
TAVR



Number at risk

Male	201	173	159	143	135	126	117
Female	147	132	122	118	112	106	101

SAVR

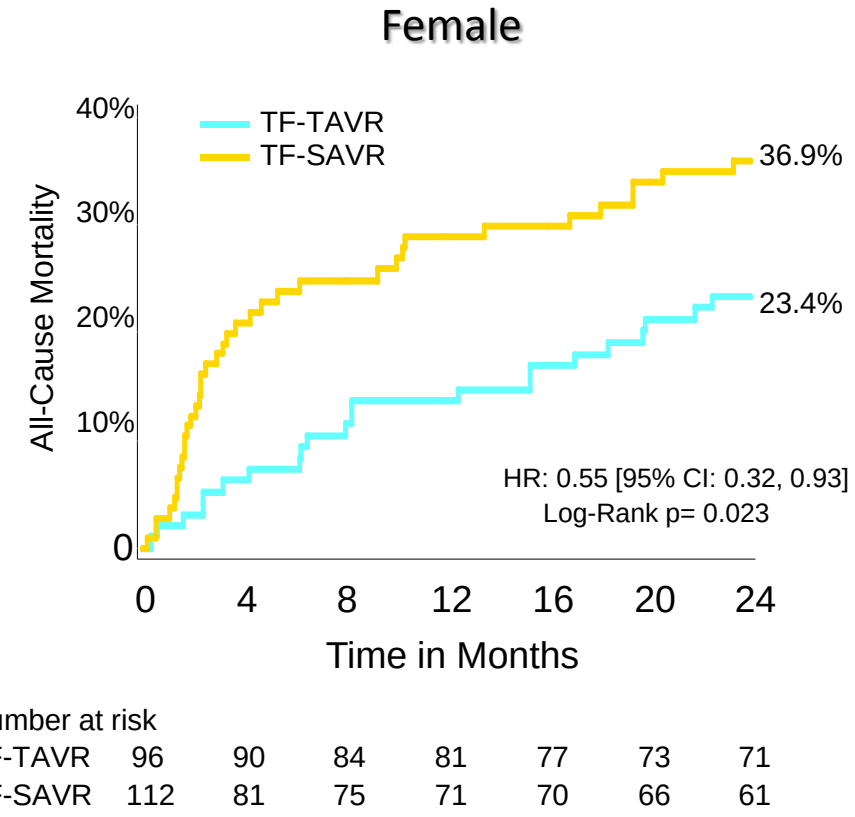


Number at risk

Male	198	156	145	139	133	128	119
Female	153	110	101	97	94	89	80

Mortality Stratified by Gender

Transfemoral Arm – PARTNER Trial



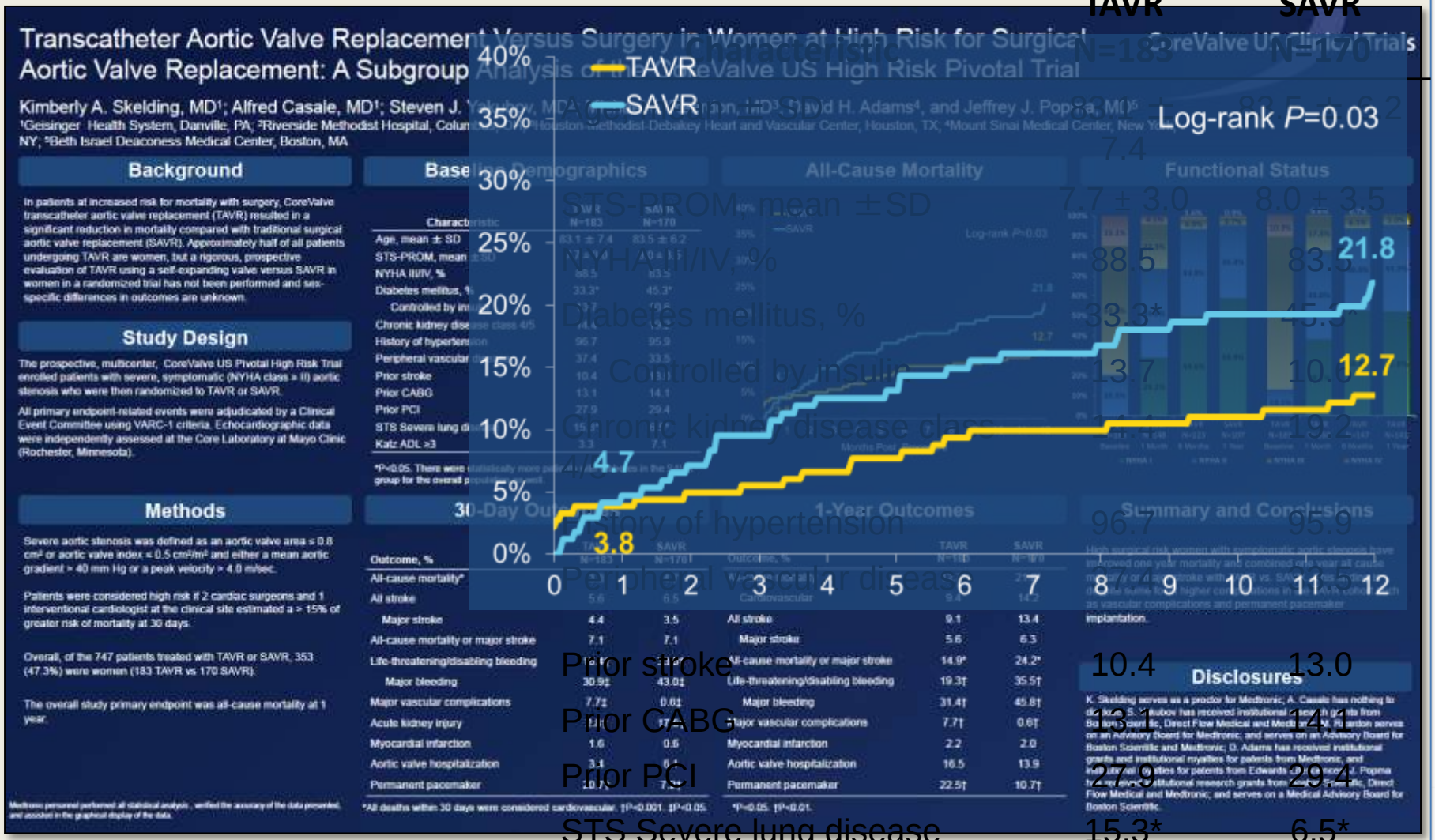
Female Gender

30 day Outcome	TAVR (N=147)	SAVR (N=153)	p
All mortality – %	6.8	13.1	0.07
All Stroke – %	5.4	0.7	0.02
Vascular complications			
Major – %	15.0	4.6	<0.01
Unplanned Art Procedure -%	18.4	3.9	<0.0001
Major bleeding - %	10.9	21.6	0.01
New PM – %	4.8	6.5	0.51
MI – %	0.0	1.3	0.50
Acute kidney inj* – %	3.4	6.5	0.21

Number at risk
TF-TAVR 148 130 121 108 102 97 91
TF-SAVR 136 105 99 97 92 88 83

Williams et al, TCT 2012

TAVR in High Risk Female Patients



Characteristic	TAVR N=183	SAVR N=170
STS-PROM, mean ± SD	7.7 ± 3.0	8.0 ± 3.5
NYHA III/IV, %	88.5	83.5
Diabetes mellitus, %	33.3*	45.3*
Controlled by insulin	13.7	10.1
Chronic kidney disease class 4/5	19.2	19.2
History of hypertension	96.7	95.9
Peripheral vascular disease	37.4	33.5
Prior stroke	10.4	13.0
Prior CABG	13.1	14.1
Prior PCI	27.9	29.4
STS Severe lung disease	15.3*	6.5*
Katz ADL ≥3	3.3	7.1

WIN TAVI Registry

Women's International Transcatheter Aortic Valve Implantation Registry

WIN TAVI Registry

Women's INternational Transcatheter Aortic Valve Implantation Registry

Aims

To determine the safety and performance of transcatheter aortic valve implantation (TAVI) according to Valve Academic Research Consortium (VARC 2) and Bleeding Academic Research Consortium (BARC) definitions in the female population.

Specific gender related issues will be investigated.

Population

All female patients (n=1,000) with severe aortic stenosis undergoing TAVI with commercially available valves and delivery systems in participating sites.

WIN TAVI Registry

Women's INternational Transcatheter Aortic Valve Implantation Registry

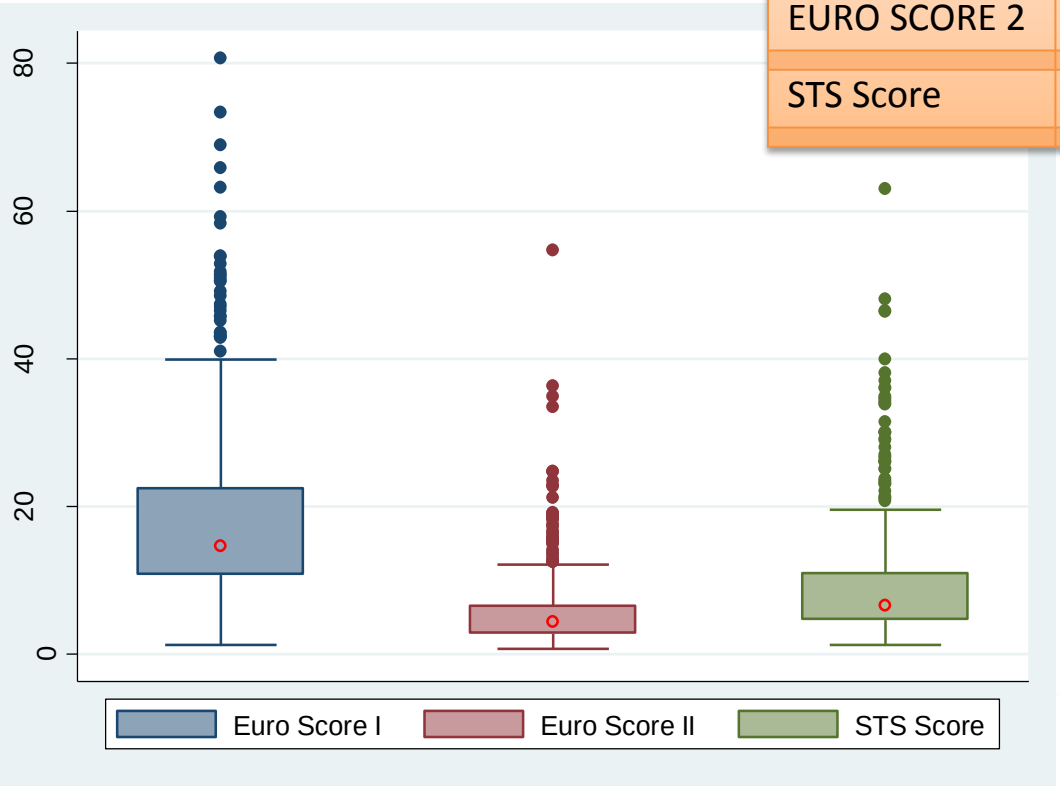
Total enrollment & enrollment by site

Total eligible - august 25 2014	520
Institut Hospitalier Jacques Cartier	84
Clinique Pasteur	70
University of Munich	60
San Raffaele Hospital	59
University of Pisa	45
Istituto Clinico Humanitas	43
University of Rome	35
University of Catania	28
University of Siena	18
Imperial College	16
Mauriziano Hospital	17
Erasmus Medical Center	14
University of Padova	12
Hospital Universitario Miguel Servet	9
Radboud University Nijmegen Medical Center	5
Elisabeth-Krankenhaus	4
Queen Elizabeth Hospital	1

WIN TAVI Registry

Women's INternational Transcatheter Aortic Valve Implantation Registry

Risk Scores	nr	Median - IQR
EURO SCORE 1	500	14.61 [10.74-22.49]
EURO SCORE 2	500	4.32 [2.77-6.58]
STS Score	372	6.6 [4.60-10.95]



Conclusions

- Compared to males, females have higher rates of vascular and bleeding complications
- There is not a significant difference in 30 day mortality between males and females
- Male sex is a predictor of one year mortality
- Women have a survival benefit up to two years with TAVR compared to SAVR particularly if performed from a transfemoral approach.
- While female sex may be a risk factor for surgical AVR, it does not appear to be a risk factor for TAVR